Peripheral Medical Centers in Israel: Narrowing the Gap – A Personal Perspective

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I would like to start this paper with some definitions in order to clarify the concepts of center versus periphery. I will also describe my own experience, which exemplifies this difference.

Peripheria is an ancient Greek term used to denote the outside. In geographic terms we usually speak about the periphery in the context of cities and regions. The periphery is usually the less developed part of a town or region, mostly located at the outer edge and far from the developed, more sophisticated and often attractive and well-tended center of the city or region [1,2].

THE CENTRAL PLACE THEORY

In 1966 the German geographer Walter Christaller proposed the 'Central Place Theory' which attempts to explain the number, size and location of human settlements in a residential system. The Central Place is a geographic location where services and goods are provided to a surrounding area. Hence the assumption that the concentration of large populations in cities is the result of the spatial organization of secondary and tertiary activities that can be conducted more profitably when clustered together rather than dispersed. It is important here to introduce some concepts that describe the concept of centrality. The first is the 'range' of an item. This is the maximum distance a customer will travel to purchase that item alone. The second is the 'threshold' for an item: the minimum volume of business necessary for an establishment selling that item alone to be commercially viable [3]. This raises a general rule: the more facilities and activities in an area, the larger the providing area. The providing area is the maximum area to which people will go for a particular service. So, centrality is about the number of activities in a certain place. Centrality also relates to the number of connections in a certain area. The more and heavier the connections and the number of activities, the higher the level of centrality of a certain area or place. This brings us to the hierarchy of places and areas that Christaller created. Thus, centrality is the level at which a place is central in relation to surrounding places, based on the number of activities and the number of connections. He talks of the 'green area', which is the third-order or tertiary area that has a low centrality with a few connections and low activity per connection. What follows is the 'red area', the second-order or secondary area that is more central with more connections but low activity per connection. And finally, the 'blue area' – the first-order or primary area, which has a high centrality with more connections and high activity per connection [4].

PERIPHERY IN MEDICINE

The concept "Peripheral medical center" is not found in any regular dictionary or medical dictionary. Instead, the medical community uses the terms "primary medical center" or "primary care" vs. secondary and tertiary (the best) medical care.

IS THERE A MEDICAL PERIPHERY IN ISRAEL?

How do we define and decide whether a medical treatment given in a certain hospital is considered good high-quality medical care, and when it is not? How do we define a "good physician"? How do we decide whether one physician is better than another? What makes a medical center a "high-quality medical center"? Is it the presence of more magnetic resonance imaging devices, more computed tomography scans, a more sophisticated catheterization laboratory, or a more sophisticated biochemical laboratory? Or perhaps it is all dependent on the quality (of training) of the physicians who work in that medical facility? How many fellowships have they done in medical centers in North America, where they were exposed to cutting-edge science and medicine? Is it dependent on the physicians' academic rank? Does it depend on their publications and the H-index score? (a metric to measure both the productivity and citation impact of the publications of a scientist or scholar, devised in 2005 by physicist Jorge E. Hirsch).

At an international meeting 5 years ago, I learned the European definition of a "Peripheral town." A peripheral town is considered a town that does not have an opera house, does not have a railway station, does not have a university campus. Would this apply also to the medical centers in Israel? Should the hospitals in the Galilee be upgraded because of the new

infrastructure of railroads and railway transportation to the north of the country? Without question, railway travel shortens distances, making us "a small global village," but will it change the definition of center and periphery? At the same time, the central cities in Israel are becoming more crowded, more sophisticated, with more, better and newer medical facilities and devices, and a greater capability to hire physicians with a better medical education and experience acquired in the foremost medical facilities in the United State and Canada. Which means that the metaphorical distance between center and periphery is becoming more significant over time, and the gap is expanding, especially since advanced medical treatment is becoming increasingly more dependent on high-tech technologies and cutting-edge science that only affluent facilities (located in the center of Israel) can afford.

HOW CAN WE NARROW THE GAP?

- **Periodic sabbaticals and fellowships**

As a young physician I had the opportunity to work in tertiary centers in Israel, to meet highly motivated "hungry" young physicians and scientists, and to develop a field in medicine that I still cherish – namely, immunological and inflammatory aspects of cardiovascular disease and atherosclerosis. It started with a series of studies that explored the possibility that acute myocardial infarction and unstable angina pectoris are due to an autoimmune process, based on clinical observations of similarities between the clinical natural history of atherosclerosis and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. It began with the clinical observation of patients admitted with an acute myocardial infarction and normal coronaries on coronary angiogram. The clinical scenario was similar to an infection or an inflammatory burst [5]. Then we found that pro-inflammatory cytokines and T-lymphocytes are activated and may have an active role in unstable angina pectoris and atherosclerosis [6]. We even showed that these data can be used as a clinical tool to assess and follow patients with unstable angina, by following T-lymphocyte activation in angina pectoris and following percutaneous transluminal coronary angioplasty (PTCA) (published in *Circulation* 1995 when I was a fellow in Cardiology) [7]. Then we found that an autoimmune response and increased levels of serum amyloid type A (SAA) characterize patients with unstable angina pectoris with high specificity and sensitivity. Levels of serum amyloid A that increased > 100% 24 hours after angioplasty may serve as a marker of restenosis [8,9].

Working in the National Institutes of Health (NIH) enabled me to advance my ideas and thoughts and to publish dozens of papers in top-league journals [10-16]. No doubt exposure to a wide range of scientists and physicians with different subspecialties stimulated and created the right atmosphere to read, think and write about our new findings and thoughts. Was it the social milieu? The advanced techniques? Or the diversity of the "hungry" scientists and the highly specialized physicians?

I returned to Israel from the NIH in 1999 to head the Department of Medicine at the Baruch Padeh Medical Center in Poriya, just outside the town of Tiberias in the Galilee. Clinically, it was a good hospital, where patients receive a sound medical evaluation and treatment according to the standard of care determined by Israel's Ministry of Health. Having served my residency at Hadassah Medical School, I always wondered about the difference between Hadassah and Poriya – from the patient's view and from the medical treatment point of view – and I could not find real differences when facing a patient admitted to the department of medicine who required a medical diagnosis and treatment for unstable angina pectoris, acute myocardial infarction, diabetes mellitus complications, infections, or other ailments. For those patients for whom I could not find a solution I was always willing to take advice from more experienced physicians from other medical centers. But that might have been the same had I been working in a tertiary center as well.

What is the fundamental difference between working in the NIH and Israel? I attribute it to the ability to ask questions, and to try to answer these questions by conducting research – clinical, basic, or translational.

I decided to apply all the knowledge I had acquired over the years, in Israel and in the USA, to the Department of Medicine and the laboratory facilities (regular biochemistry and hematological labs) that we had at the time. Thanks to that initiative we began to ask questions and to answer them by conducting clinical research as well as translational research based on the skills that I had gained at the NIH. And we published numerous papers [17-31], with the deep-felt sense that this was pioneering work, as if we were initiating something that had not existed in the past, and we proved that it could be done.

- **Is it a question of initiative and scientific drive?**

But this was not enough. So I went for another round at the National Institutes of Health, learned new techniques in stem cell technology [32-43], and returned to implement them at home. My plans were met with considerable doubt: grow stem cells in Poriya? These initial misgivings eventually passed and we did indeed do it. We grew colonies of stem cells and conducted research in stem cells and vascular biology, focusing on translational research in vascular biology. And after 6 years I had another round in the USA, at the University of Miami where I gained more clinical and research experience in stem cells.

- **Academic affiliation**

On my first return from the NIH in 1999 we were at that time affiliated with the Technion Faculty of Medicine in Haifa, and we started to teach medical students. Teaching is an effective way to keep up with new discoveries, to be updated, and to maintain a high clinical level both academically and professionally. Still,

research was not available in the neighborhood. In 2012 that affiliation ended, and since then we have been affiliated with Bar Ilan University (Azrieli Faculty of Medicine) in Safed. For the first time we could sense the difference. Bar Ilan University built seminar rooms with up-to-date equipment for teaching medical students in every department, built (together with the Padeh Medical Center) a well-equipped research institute where several laboratories began to do clinical and basic research in nephrology, diabetes mellitus, infectious diseases, cardiology, cancer, and stem cells, enabling all the clinical departments (Ophthalmology, Periodontology, Surgery, Orthopedics, Pulmonology, Cardiology) to take an active part in clinical and basic research using advanced tools (such as PCR and micro-RNA processing). Clearly, research is an essential means of narrowing the gap in education and knowledge, allowing everyone a fair chance to explore new avenues.

- **Academic meetings combining tertiary centers and primary care centers**

We recently hosted an international meeting with European scientists and physicians – a rare event for our medical center. The participants came to share their experience, knowledge, and their most recent findings. This special event – the 7th Italy-Israel Symposium of Autoimmunity and Rheumatology – was organized by the Zabludowicz Center for Autoimmune Diseases at Sheba Medical Center in Tel Aviv. Professors Yehuda Shoenfeld and Howard Amital believed it would be interesting for this international group to see and explore another medical center in Israel, one not in the city or the center of the country. This way, science and knowledge were brought to *our* door, and all we had to do was enjoy the talks – on endothelial stem cells in rheumatoid arthritis, on scleroderma and cardiovascular complications, on systemic lupus erythematosus in pregnancy, and on the significance of high titers of autoantibodies in the body even years before disease onset.

The opportunity to discuss issues of clinical and scientific importance, to have a "brainstorming" event at home was a new and refreshing wind of goodwill coming from the center of Israel. Perhaps it will stimulate a new trend in the country – that the well-established tertiary centers will share their abilities and knowledge, share friends and international connections, with centers located far from Tel Aviv. This will bring knowledge and friendship, it will narrow the gap between the well-established tertiary medical centers and centers located more than 100 kilometers from Tel Aviv and Jerusalem, and offer hope for better medicine and medical care of patients who live in the north of Israel.

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Capsule

The secret(ing) life of the tumor stroma

Hypoxic solid tumors develop a dysfunctional vasculature that prevents efficient chemotherapeutic penetration. **Kugeratski** et al. analyzed the proteome and secretome of cancer-associated fibroblasts, a prominent cell type in the tumor stroma. Hypoxia increased the levels of a protein called hypoxia-induced angiogenesis regulator (HIAR) in cancer-associated fibroblasts. HIAR promoted the release of the pro-angiogenic factor VEGF from these cells and induced VEGF-dependent signaling in endothelial cells. Thus, HIAR could be targeted by anti-angiogenic therapy, which has been unsuccessful when directly targeting VEGF signaling.

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Capsule

Akkermansia muciniphila is permissive to arthritis in the K/BxN mouse model of arthritis

Studies have identified abnormalities in the microbiota of patients with arthritis. To evaluate the pathogenicity of human microbiota, **Stoll** and group performed fecal microbial transplantation from children with spondyloarthritis and controls to germ-free KRN/B6xNOD mice. Ankle swelling was equivalent in those that received patient vs. control microbiota. Principal coordinates analysis revealed incomplete uptake of the human microbiota with over-representation of two genera (*Bacteroides* and *Akkermansia*) among the transplanted mice. The microbiota predicted the extent of ankle swelling (R2 = 0.185, P = 0.018). The abundances of *Bacteroides* (r = –0.510, P = 0.010) inversely and *Akkermansia* (r = 0.367, P = 0.078) directly correlated with ankle swelling. Addition of *Akkermansia muciniphila* to Altered Schaedler's Flora (ASF) resulted in small but statistically significant increased ankle swelling as compared to mice that received ASF alone (4.0 mm, 3.9–4.1 vs. 3.9 mm, IQR 3.6–4.0, P = 0.041), as did addition of *A. muciniphila* cultures to transplanted human microbiota as compared to mice that received transplanted human microbiota alone (4.5 mm, IQR 4.3–5.5 vs. 4.1 mm, IQR 3.9–4.3, P = 0.019). This study supports previous findings of an association between *A. muciniphila* and arthritis.

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