Edgar Pick, M.D.,Ph.D.

An analysis of the roots of Edgar Pick's affinity for experimental science might reveal a link to having worked as a laboratory technician in a tuberculosis hospital, when forced to interrupt his medical studies while waiting to get permission for leaving his native Romania for Israel. The "mycobacterial expertise" turned out to be useful for finding employment in the laboratory of the Hansen leprosy hospital in Jerusalem prior to continuing his medical studies at the Hebrew University Hadassah Medical School. Who would have guessed that this might have influenced his future interest in cell-mediated immunity?

Edgar's introduction to basic research took place when he volunteered, as a medical student, to learn the primary elements of the trade in the laboratory of the immuno-hematologist David Nelken. His first paper, on an immunological method (never to be used), appeared in *Nature*, at a time when a sixth year medical student still had a fair chance of his work being published in the illustrious journal.

Deciding to become an immunologist, he went for postdoctoral training to one of the Meccas of bio-medical research, the Scripps Research Foundation in La Jolla, unsuspecting that, years later, the august institution will become a center of research on the very subject that became Edgar's lifelong focus, housing the laboratories of Bernard Babior, John Curnutte, Gary Bokoch, and Andrew Cross.

A chance encounter with John Turk who, in the sixties of past century, was the Pope of cell-mediated immunity (then, labeled by the long forgotten term "delayed hypersensitivity"), brought him to London, where the transition from an immunologist to a biochemist took place, expressed in his lasting preference to work with molecules and reductionist *in vitro* systems. This was the starting point of Edgar's interest in cytokines (called lymphokines, at the time), which was also the subject of his Ph.D. thesis at the University of London (with the legendary Ivan Roitt as the examiner), and became a central theme of his research on joining Tel Aviv University. Edgar was the coauthor, with John Turk, of one of the first reviews on cytokines, a coeditor of the book "Biology of the Lymphokines", and the editor, with Maurice Landy as advisory editor, of the 15-volumes series "Lymphokines". Curiosity about the molecular basis of macrophage activation by a cytokine (known through the work of Carl Nathan to be interferon γ) was the stimulus that led to the NADPH oxidase becoming the epicenter of his research for four decades. This was rooted in the work of Zanvil Cohn, showing that the molecular basis of macrophage activation was an enhanced ability to generate reactive oxygen species (ROS) in response to phagocytosed microorganisms.

Edgar's seminal discovery, with student Yael Bromberg, was the finding that the NADPH oxidase (briefly, oxidase) of phagocytes consisted, in addition to the membrane-associated catalytic unit, the existence of which was known, of cytosolic components. A combination of membrane and cytosol of resting phagocytes exposed to long-chain unsaturated fatty acids (such as arachidonic or oleic acids) or some anionic detergents (such a sodium or lithium dodecyl sulfate) generated ROS *in vitro* upon addition of NADPH. This became known as the "cell-free system" and similar systems were described by Roger Heyneman, Linda McPhail, and John Curnutte, proving the truth of the statement by Thomas Kuhn that "a significant scientific novelty so often emerges simultaneously from several laboratories". The discovery led to the identification of the cytosolic components

p47^{phox} and p67^{phox} by Robert Clark and William Nauseef and by Harry Malech and coworkers, and revealed the molecular mechanism of some forms of Chronic Granulomatous Disease.

With the purpose of identifying functionally important regions in individual oxidase components, Edgar, Gili Joseph and Iris Dahan introduced "peptide walking", which also served as a path to the discovery of peptide-based oxidase inhibitors, with a yet to be realized potential for clinical application.

Edgar and Arie Abo purified the “third cytosolic component” from macrophages and established its identity with the small GTPase Rac1 and its presence in the cytosol as a complex with RhoGDP dissociation inhibitor (RhoGDI). Edgar and Yelena Ugolev established the role of anionic membrane phospholipids and guanine nucleotide exchange factors (GEFs) in the dissociation of [RacGDP-RhoGDI] complexes. The identification of Rac1 was paralleled by that of Rac2 in neutrophils by Ulla Knaus and Gary Bokoch.

Cell-free activation offered a unique opportunity to establishing that cytochrome b_{558} was the ”one and only” membrane component of the oxidase and that no other flavoprotein participated in ROS generation. Starting with the use of lipids from egg yolk by Iris Dotan and followed by the careful analysis of phospholipid specificity by Sally Shpungin, activation of purified cytochrome b_{558} *in vitro* was made possible by its incorporation in liposomes consisting of cell-derived or synthetic phospholipids, a procedure universally applied and described in a rarely cited paper.

Hosting the biophysicist Vasilij Koshkin in the Pick laboratory was at the origin two discoveries. One was proving that the oxidase could be activated by p67^{phox} in the absence of p47^{phox}, supporting the paramount role of p67^{phox} (an idea pioneered by David Lambeth). The second was direct evidence for the proposal by Anthony Segal and Daniel Rotrosen of the presence of all redox stations in cytochrome b_{558}, demonstrated by the ability to elicit ROS production by cytochrome b_{558} incorporated in liposomes rich in phosphatidic acid, in the absence of cytosolic components.

Edgar’s group is known for the pioneering design, with Yevgeny Berdichevsky and Ariel Mizrahi, of the tripartite chimeras ("trimeras"), in which functionally important segments of the cytosolic components p47^{phox}, p67^{phox}, and RacGTP were fused in a single molecule, capable of activating the oxidase *in vitro* and *in cellulo*.

Edgar’s most recent work, with Edna Bechor and Anat Zahavi, was centered on the finding that p67^{phox} existed in an autoinhibited state due to the presence of intramolecular bonds. Interaction of p67^{phox} with RacGTP caused disengagement of the bonds and enabled binding of modified p67^{phox} to a specific site in the dehydrogenase region (DHR) of Nox2, located between the FAD- and NADPH-binding sites. This is likely to result in a conformational change in the DHR facilitating electron transfer between redox stations. Progress in the burgeoning cryo-EM field is eagerly expected to confirm this model.

Edgar Pick is Professor Emeritus at Tel Aviv University and a former Director of the Cohheim – Minerva Center for Cellular and Molecular Phagocyte Research.

Edgar was a member of the Editorial Boards of numerous international journals, including a stint as a Section Editor for the *Journal of Leukocyte Biology*. He is a member of the Society of Leukocyte Biology, the American Society of Biochemistry and Molecular Biology, the American Association of Immunologists, the American Association for the Advancement of Science, and the Israel

Immunological Society. He has been a regularly invited speaker and/or session chair at numerous international meetings centered on phagocytes and NADPH oxidases, most notably the Gordon Research Conferences.

Edgar has published 114 peer-reviewed articles, 10 chapters in books, and 19 papers in Conference Proceedings, and has co-edited and edited 2 books and 11 volumes in a thematic book series.