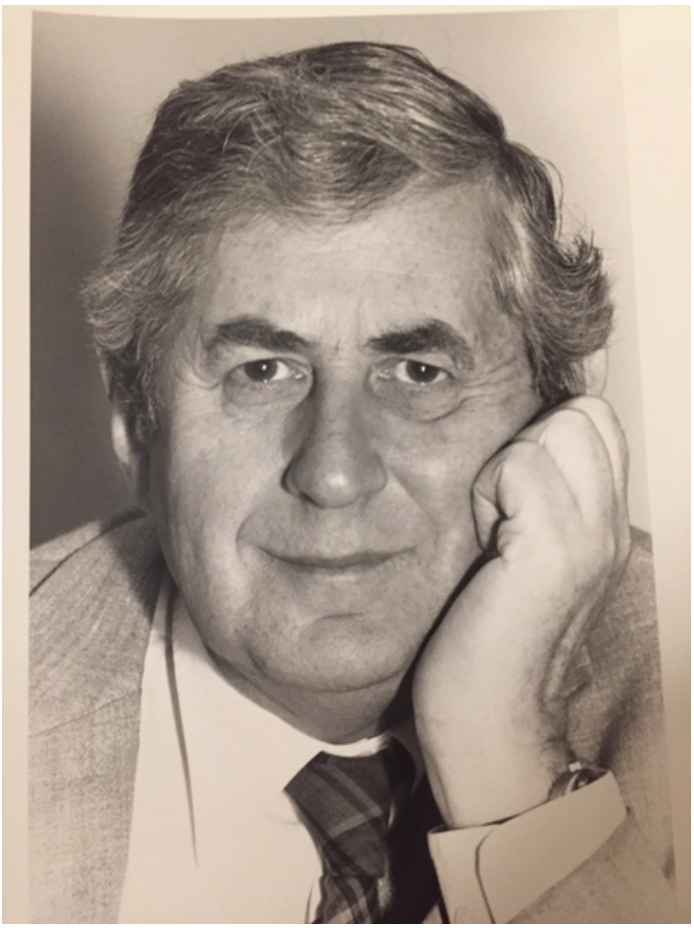
THE FACULTY OF MEDICINE
Harvard University

Morris J. Karnovsky



A Pore Poem – A Rich Life

Morris Karnovsky, M.B.B.Ch, D.Sc.

The amazing John Pappenheimer,
(Whose name defies any rhymer!)
And many others, postulated small and large pores to be
The basis of capillary permeability
I, perhaps foolishly, ascribed small pore function
To the endothelial junction
Which I opined is incompletely tight
But I was told this is not right!
Suppose there are also rare gaps, sufficiently large
Thru which big macromolecules can barge
Others fervidly disagree, And localize to Palade's caveolae
Not only large, but small pores as well!
What is correct? Will time tell?
Will this 35 year old dispute
Be one day rendered mute?

This poem, written by Prof. Morris J. Karnovsky, Shattuck Professor of Pathological Anatomy at Harvard Medical School, illustrates much about this wonderful man. He was not only an innovator of the highest form, a scholar unafraid to challenge dogma, but also a man of letters and of great humor who despite his amazing accomplishments never missed an opportunity to make fun of himself first. Morris departed January 2018 at the age of 91 and it was our great loss.

Few scientists have had as great an impact on medicine as Prof. Karnovsky. His discoveries span the breadth of medical science and his inventions have changed medical research and diagnostics. The chemical reactions he intuited made it possible to stain tissue biopsies not simply based on dye uptake but

In tribute to their dedicated efforts to science and medicine, deceased members of the Harvard Faculty of Medicine (those at the rank of full or emeritus professor) receive a review of their life and contributions with a complete reflection, ***a Memorial Minute****.*

also on the basis of binding of stains to specific proteins. His contributions to immunohistochemistry forever changed science and his commitment to his students and colleagues transformed countless lives and careers.

Karnovsky was born in Johannesburg, South Africa. His father became one of the first pharmacists in the country and his mother was an opera singer whose family hosted world leaders in arts and music. Indeed, Karnovsky played the piano on the lap of Sergei Rachmaninoff – retaining forever a love for music. Years later, he insisted that his laboratory together watch the transmission of Vladimir Horowitz performing after a lengthy exile from Russia, and then remarked with great insight as to the unique unbent positioning of Horowitz's fingers as he played, explaining that this created a key strike that produced pure and consistent tones. Educated at the King Edward VII School in Johannesburg, Morris became a life-long devotee of art, literature, and especially poetry, philosophy and natural sciences as well as community.

His commitment to community was evident from the earliest age. In high school, Karnovsky organized an evening medical clinic for blacks and in medical school at the University of Witwatersand he actively protested segregation and provided medical care in an African Township. Graduating in 1950 with an M.B.B.Ch., he continued his clinical work in the township as he simultaneously advanced science at an incredible pace receiving his D.Sc. - working closely with classmate 2002 Nobel laureate Sydney Brenner. Of note they both interned in the Department of Anatomy at Witwatersrand directed by Raymond A. Dart, discoverer of Australopithecus africanus (the Taung Child). Later they, with Lewis Wolpert the well-known British developmental biologist, sought further training in London. Morris trained at the Hammersmith and the Royal Cancer Hospitals, mastering the emerging science of cytochemistry. In 1955, he made his way to Harvard Medical School where he worked with Arthur Hertig Chair of the Department of Pathology. He was an assistant resident pathologist at Beth Israel Hospital, afternoon and nights, and taught Medical Science 201ab in the mornings. This comprehensive year-long course in all the basic sciences, including general Pathology, was required of all graduate students at Harvard Medical School and from that time forward Karnovsky never stopped teaching or conducting research.

His contributions to Harvard Medical School are legendary. Through the more than forty years Morris was a member of the faculty he was repeatedly called upon to serve in every conceivable role, especially through times of hardship, controversy or vacuums of leadership. His internationally renowned research laboratory guided the careers of scores of research fellows, students and faculty at all stages (all of whose personal histories he remembered to the end in detail). He designed the HMS Cell and Developmental Biology Program, which he led for 14 years, and on two separate occasions - for a total of more than four years - served as interim chair of the Department of Pathology. He developed educational initiatives that have become models around the world, chaired important student-faculty committees, and led the fight for student services and advocacy. He, his brother Manfred and close colleague Clifford Barger not only advocated for admission of underrepresented populations to Harvard

Medical School, these three giants of science also provided weekly extracurricular lectures for those admitted – a quiet contribution that runs the risk of being forgotten as the last of this trio has passed on.

Karnovsky loved his family, and was fiercely proud of the accomplishments of his son David and daughter Nina, and their children; he treated the dozens of students and trainees he mentored the same way. That those he nurtured have gone on to have outstanding and productive careers as scientists and clinicians in their own right gave Karnovsky more satisfaction than any of his own discoveries and achievements. As his students, we inherited not only his method of critical thought, communication skills and approach to science, but tangible gifts as well. Morris had a keen eye for art and hung the pieces he and his darling wife Shirley had collected in the offices of his postdoctoral fellows. When this art was appreciated, it departed with the postdoctoral fellow – he joked that they were on permanent loan from the Shirley and Morris J. Karnovsky collection. During the last few months of his life, he cherished the many visits and calls from his students, asking about their latest research discoveries and catching up on their personal lives.

Karnovsky was, above all, a towering intellect of prodigious productivity—he is the most quoted author in pathology and the sixth most widely quoted author in all of medicine. Two common threads bind Morris' research through the years -- the study of the structural components of cells and their function, and the analysis of how disease states change structure and function. His research pioneered the invention and development of different technologies and was often an elegant weave of innovative methods, creative experimental techniques and sophisticated models.

One of Morris' most widely recognized contributions was the application of the horseradish peroxidase (HRP) tracer method of Werner Straus to both the light and electron microscopy, by introducing diaminobenzidine (DAB) as an electron donor. The first paper to report this technique authored by Morris Karnovsky and Richard Graham traced the endocytic uptake of HRP from the glomerular filtrate into cells of the proximal tubules. This study is not only a citation classic, but it is also one of the most highly quoted studies in the biomedical literature having now been cited some 8000 times. In fact, six of Morris' papers are "citation classics," having been cited more than 1,000 times. He persevered in his ultrastructural studies despite the local Longwood fluctuations in line voltage that challenged the functioning of the electron microscope – and in true Morris spirit let everyone know, explained and examined the phenomenon in detail and then mocked in verse.

With Thomas Reese, Morris used the HRP method to establish that the endothelial cells in the brain vasculature form the cellular basis of the so-called blood brain barrier. This endothelial barrier prevents macromolecules in the blood from reaching neurons. Likewise, with Elio Raviola, Morris established the blood-thymus barrier, and with Eveline Schneeberger, the blood-air barrier of the lungs. The small pore system of Pappenheimer was identified in muscle capillaries at the level of permeable intercellular junction, an observation that remains controversial (see poem above).

Another innovation developed by Morris was the introduction of colloidal lanthanum as an electron opaque tracer. Using this, Morris and Jean-Paul Revel succeeded in revealing the fine structure of gap junctions, the structural correlate of electrophysiologically defined electrical synapses that were known to occur in cells of excitable tissues. Morris advanced a number of other cytochemical techniques including methods to detect mitochondrial cytochrome c oxidase, cholinesterases, and oxygen derived products of the oxygen burst. With Richard Rodewald, he described the slit diaphragm of the glomerulus, and with Graeme Ryan, he demonstrated that the glomerular basement membrane serves as the barrier to endogenous albumin.

Later, Morris brought all of these methods and perspectives to describe the vibrancy of the endothelium, erasing by elegance of his work the conventional view of this structure a passive physical barrier to reveal the dynamic regulatory organ we recognize today. This basic science paved the way for interventional cardiology innovations like stents and their drug-eluting counterparts.

Though one of the most acknowledged scientists in history, Karnovsky did not seek fame or fortune – he refused to patent ideas that he felt should be in the public domain. The diaminobenzidine (DAB) method and Karnovsky fixative are worth hundreds of millions, yet Morris felt they belonged to the public and went to great lengths to ensure unfettered access. He never wrote a paper on his fixative because he preferred to give away the recipe.

Karnovsky's unique perspective on and approach to research was reflected in his service and awards. He was President of both the American Society of Cell Biology, the premier basic science organization, and the American Association of Pathologists, a leading clinical organization, and his honors run the gamut from the Benditt, Rous-Whipple, E.B. Wilson, and the Gold-Headed Cane awards. Similarly, he served on the editorial boards of The Journal of Cell Biology, and The American Journal of Pathology, among others. He was the Maude Abbott Lecturer of the US and Canadian Academy of Pathology, member of the National Academy of Medicine and American Academy of Arts and Sciences, Fellow of Royal Microscopy Society, and on and on; while he was grateful for what these awards represented, these accolades remained in his drawer.

Karnovsky was a giant in the realms of experimental pathology and cell biology, a dedicated father and husband, committed teacher, precise and creative genius, and a true renaissance man. He leaves a legacy of scholarship, mentoring, and service that is rarely achieved and hard to surpass.

Respectfully Submitted,
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