CC/NUMBER 46
NOVEMBER 13, 1989

This Week's Citation Classic®

Cereijido M, Robbins E S, Dolan W J, Rotunno C A & Sabatini D D. Polarized monolayers formed by epithelial cells on a permeable and translucent support. *J. Cell Biol.* 77:853-80, 1978.

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An epithelial cell line (MDCK) was used to prepare monolayers that, *in vitro*, develop properties of transporting epithelia. Monolayers were formed by plating cells at high densities (10^6 cells/cm^2) on collagen-coated nylon cloth disks to saturate the area available for attachment, thus avoiding the need for cell division. An electrical resistance developed within 4-6 hours after plating and achieved a steady-state value of 104 ± 1.8 Ω·cm^2 after 24 hours. [The *SCI*® indicates that this paper has been cited in over 360 publications.]

Epithelial Differentiation and Exile

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August 7, 1989

In 1968, after 15 years of research with transporting epithelia, I found it more difficult to discover an exciting new question than a trivial new answer. However, I realized that, in spite of the enormous amount of information available, we still ignored how epithelial cells acquire their two basic features, i.e., their *tight junctions* that confer the ability to act as effective permeability barriers and their apical/basolateral *polarity* that allows them to exchange substances between the organism and the environment.

With my coworkers Caty Rotunno and Edith Zylber, we disassembled natural epithelia, using trypsin-EDTA, and plated the cells on filter paper, hoping that they would reconstitute a transporting epithelium.[1] But the cells did not even attach to the filter. Then, we learned that Dr. Joseph Leighton (Pittsburgh) attributed the blisters formed in monolayers of MDCK cells to vectorial transport and accumulation of fluid under the monolayer. So we decided to culture MDCK cells on a permeable support. Yet, we did not know how to culture MDCK cells, nor any other cell type for that matter.

David Sabatini (New York University Medical School) had to travel to Argentina (his father had died) and offered to teach me how to work with cultured cells. So I obtained a Guggenheim Fellowship and went to Sabatini's lab (1974) and, with him and his team (E.S. Robbins and W.J. Dolan), succeeded in culturing MDCK cells, this time on a disk of a nylon cloth. It behaves in many respects as a natural transporting epithelium. One of the main advantages of this preparation is that it polarizes and makes tight junctions in a few hours, under conditions amenable to experimental control. I gave seminars in the US and Europe, Caty also obtained a Guggenheim Fellowship (1975) to perform further work, and my coworkers Carlos Rabito (now at Massachusetts General Hospital) and Enrique Rodriguez-Boulan (now at Cornell University) went to work with Leighton and Sabatini, respectively. However, due to political upheaval, our laboratory in Buenos Aires was disbanded.

Argentinean history shows a long succession of military dictatorships. Each one forces a large number of scientists out of the country, so that the Argentinean scientific community in the US is much larger (as measured by number and relevance of publications) than the one in Argentina itself, let alone the number of Argentinean scientists scattered in Europe. Thus Dr. César Milstein, an Argentinean who won the Nobel Prize for developing monoclonal antibodies, is in Cambridge, not in Buenos Aires.

J. Huxley has said that the history of science is a long struggle against the Principle of Authority. I used to publish articles in magazines and newspapers in which I maintained that when a country abides by the Principle of Authority, it can develop neither science nor democracy. Such articles, together with my association with colleagues to promote science and democracy, put me at a disadvantage with the authorities. I received phone calls and letters threatening my life, and two months after the Military Junta of 1976 took power, my coworker Rotunno and I were fired "for administrative reasons" (*sic*) from the National Research Council of Argentina (CONACYT). We were career investigators of CONACYT, an institution founded in 1957 by Nobel Prize winner Bernardo A. Houssay, which paid 100 percent of our salaries and those of three younger coworkers, as well as supported our research.

We were forced into exile, and our papers only started to be published four years after we developed our preparation. In the meantime Dr. Dayton S. Misfeldt and coworkers published a similar finding.[2]

The monolayer of MDCK cells opened entirely new avenues in epithelial research, and now we have an idea on how cells polarize[3] and make tight junctions.[4,5]

1. **Zylber E A, Rotunno C & Cereijido M.** Ion and water balance in isolated epithelial cells of abdominal skin of frog *Leptodactylus ocellatus*. *J. Membrane Biol.* 13:199-216, 1973. (Cited 40 times.)
2. **Misfeldt D S, Hamamoto S T & Pitelka D R.** Transepithelial transport in cell culture. *Proc. Nat. Acad. Sci. USA* 73:1212-6, 1976. (Cited 355 times.)
3. **Cereijido M, Contreras R G & González-Mariscal L.** Development and alteration of polarity. *Annu. Rev. Physiol.* 51:785-95, 1989.
4. **Cereijido M, González-Mariscal L, Avila G & Contreras R G.** Tight junctions. *CRC Crit. Rev. Anat. Sci.* 1:171-92, 1988.
5. **Cereijido M, González-Mariscal L & Contreras G.** Tight junction: barrier between higher organisms and environment. *News Physiol. Sci.* 4:72-5, 1989.

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