CC/NUMBER 42
OCTOBER 18, 1982

This Week's Citation Classic

Revel J P & Karnovsky M J. Hexagonal array of subunits in intercellular junctions of the mouse heart and liver. *J. Cell Biol.* 33:C7-C12, 1967.
[Depts. Anat. and Pathol., Harvard Med. Sch., Boston, MA]

This paper reviews some of the circumstances which led us to conclude that structures similar to 'electric synapses' also exist between non-excitable cells. Now called 'gap junctions,' 'nexus,' and 'macula communicans,' they allow for exchange of low MW solutes between contacting cells. [The *SCI*® indicates that this paper has been cited in over 865 publications since 1967.]

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August 6, 1982

"Our paper was actually the result of a serendipitous discovery. For quite a while Morris Karnovsky and I had been interested in techniques for the ultrastructural demonstration of carbohydrate-containing moieties on cell surfaces. On the hypothesis that colloidal suspensions or polymers of heavy metals might be of use, we tried, among others, the lanthanides. The complexes formed could diffuse into and act as a tracer of intercellular spaces. Morris soon produced images in heart muscle where the whole intercellular space was filled with electron opaque material. He rushed over one evening with still-wet negatives and we saw, to our surprise, areas showing a beautiful quasi-crystalline pattern of ~70 A particles when the cell membranes were viewed *en face*. I recalled the hexagonal arrays in electrical synapses after permanganate fixation,[1] and in negatively stained liver plasma membranes.[2] The subunit structure was not characteristic of the plasma membrane in general, and our 'chief,' D.W. Fawcett, agreed that we might be observing the so-called 'close' junctions in the heart. Shortly thereafter I found identical structures in a sample of liver, of course in a partially torn section which soon broke up altogether, but not before it had been triumphantly photographed.

"There followed the rapid accumulation of data, and we soon realized that depending on the angle at which one viewed the junctions, they could be seen as a series of striations, or as particles. We concluded that structures similar to electrical synapses could be seen in non-excitable tissues, and that they represented a unique type of cell junction. This, and the usefulness of the technique to demonstrate cell junctions, are two reasons our paper is still cited.

"I won the senior authorship by the toss of a coin. It should be pointed out that although we did not use the term 'gap junction,' somehow it has, over the years, been attributed to us!

"After our initial report was published we thought to put our observations into a detailed paper. Optical diffraction experiments confirmed the hexagonal packing of the particles. We made a number of plastic models with which we could reproduce all the appearances of the junctions as seen in the electron microscope. We never wrote up these results as we were soon pursuing instead the ultrastructure of the junctions as seen by the then newly introduced technique of freeze-cleaving, by which, it was hoped, further features of structure would be revealed. Besides many subtle details, it definitively showed that gap and tight junctions were clearly different structures. An excellent overview of the field is a series of short papers resulting from a symposium organized by Werner Loewenstein.[3] It is ironic to note, however, that recent rapid-freeze studies would indicate that the dramatic tight hexagonal packing we observed may represent, to some extent, an artifact of tissue preparation and fixation."

1. **Robertson J D.** The occurrence of a subunit pattern in the unit membranes of club endings in Mauthner cell synapses in goldfish brains. *J. Cell Biol.* 19:201-21, 1963.
2. **Benedetti E L & Emmelot P.** Hexagonal array of subunits in tight junctions separated from isolated rat liver plasma membranes. *J. Cell Biol.* 38:15-24, 1968.
3. **Loewenstein W R.** Introductory remarks to the symposium. *In Vitro* 16:1007-68, 1980.