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This Week's Citation Classic™

Caspar D L D & Klug A. Physical principles in the construction of regular viruses. *Cold Spring Harbor Symp.* **27**:1-24, 1962.
[Children's Cancer Res. Foundation, Children's Hosp. Med. Ctr.; Dept. Biophys., Harvard Med. Sch., Boston, MA; and Med. Res. Council Lab. Molecular Biol., Univ. Postgrad. Med. Sch., Cambridge, England]

Starting with the postulate that regular virus capsids are constructed from identical subunits by a self-assembly process, the quasi-equivalence theory explained why icosahedral symmetry should be preferred for the design of isometric capsids, and the possible icosahedral surface lattices, defined by the set of triangulation numbers, were enumerated. [The *SCI*® indicates that this paper has been cited in over 640 publications since 1962.]

Donald L.D. Caspar
Rosenstiel Basic Medical Science
Research Center
Brandeis University
Waltham, MA 02254

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"In 1956, Crick and Watson in Cambridge, England, predicted that isometric virus particles should be constructed from identical subunits arranged with cubic symmetry.[1] From the same laboratory, I reported X-ray crystallographic data providing the first evidence for icosahedral virus symmetry.[2] Aaron Klug and his colleagues in London soon showed that other isometric viruses were icosahedral, and suggested that some general principle might explain a preference for icosahedral symmetry.[3] I began a transatlantic collaboration with Klug in 1958, following Rosalind Franklin's untimely death. We first reviewed the work that she had started on the helical tobacco mosaic virus and then tried to understand the design of icosahedral viruses. Icosahedral symmetry requires 60 equivalently related parts, but for some icosahedral virus capsids, chemical data indicated *more* than 60 identical subunits, and the number of morphological units seen by electron microscopy was not a multiple of 60. The problem was to explain how to build the shells from a large number of identical units by repeating the same pattern of contact without the constraint of strict equivalence. An anticipatory key to our solution was Klug's recognition of an analogy with Buckminster Fuller's icosa-geodesic dome designs.[4]

"Early in 1962, Fuller came to lecture at Harvard University, which stimulated me to complete the models I had been building at the Children's Cancer Research Foundation in Boston, using his tensegrity principle, to demonstrate why icosahedral viruses *are* icosahedral and how the complete design could be built-in to the specific bonding properties of the parts. That year, Klug asked me to join him in writing a paper for *Cold Spring Harbor Symposium on Quantitative Biology* that was intended as an introduction to our major collaborative paper planned on design and construction of icosahedral viruses, based on my model building. In a hectic two weeks at the end of May 1962, we wrote our *Citation Classic*™ paper, which ended up incorporating much of the theory it was to have introduced. We then changed the order of our names on this paper, and never completed the proleptically referenced theory paper. The models illustrating the theory finally appeared 18 years later, in a paper of mine subtitled, 'Quasi-equivalence revisited.'[5]

"We introduced three terms in our *Citation Classic* that have been useful for describing a variety of structures: 'triangulation number,' to define the possible icosahedral surface lattice designs; 'quasi-equivalence,' to describe nearly equivalent bonding of identical units; and 'self-assembly,' to identify assembly processes controlled by the specific bonding of the parts. Citations of these terms appear to account for most of the references to our paper.

"Starting with the simple presumption that specificity of bonding among identical, but adaptable, subunits should be conserved in the self-assembly of virus capsids, our quasi-equivalence theory explained icosahedral symmetry and enumerated the possible designs. The beauty of this theory and the success of the predictions made it appear that conservation of bonding specificity was a necessity in icosahedral virus architecture—until three years ago, when Ivan Rayment, working with me, established by X-ray structure analysis that the 60-hexavalentmorphological units in the T=7 polyoma virus capsid are all pentamers,[6] instead of hexamers, as predicted on the expectation of quasi-equivalence. Understanding the significance of this result exemplifying the diversity of biological structures is now an experimental rather than a theoretical problem."

1. **Crick F H C & Watson J D.** The structure of small viruses. *Nature* **177**:473-5, 1956. (Cited 170 times since 1956.)
2. **Caspar D L D.** Structure of tomato bushy stunt virus. *Nature* **177**:476-7, 1956.
3. **Finch J T & Klug A.** Structure of poliomyelitis virus. *Nature* **183**:1709-14, 1959. (Cited 90 times since 1959.)
4. **Fuller R B & Marks R W.** *The Dymaxion world of Buckminster Fuller*. New York: Doubleday, 1960. 246 p.
5. **Caspar D L D.** Movement and self-control in protein assemblies: quasi-equivalence revisited. *Biophysical J.* **32**:103-35, 1980.
6. **Rayment I, Baker T S, Caspar D L D & Murakami W T.** Polyoma virus capsid structure at 22.5 angstrom resolution. *Nature* **295**:110-25, 1982.