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OBITUARY

Donald L.D. Caspar (1927–2021)—pioneer of virus structures

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Abstract
Donald L.D. Caspar (1927–2021) devoted his career to understanding the structure of viruses. He interacted with leading structural scientists of his time and ran top research laboratories. His discoveries cut across disciplinary lines as he established the icosahedral geometry of viruses.

Keywords Donald Caspar · Aaron Klug · Buckminster Fuller · Tobacco Mosaic Virus · Icosahedral geometry · Fullerenes · Quasicrystals

Donald L.D. Caspar (1927–2021, Fig. 1) was an American biophysicist by training, but in essence, he was a structural chemist and structural biologist. He was born in Ithaca, New York, where his father was a chemistry graduate student at Cornell University. Donald was about ten years old when the crystallographer Isidor Fankuchen [1] told him about the Tobacco Mosaic Virus (TMV) and its heretofore unknown shape. This had such an impression on the young boy that the encounter charted his road in science. He studied at Cornell and graduated with a BA in physics in 1950. He attended graduate school at Yale University and graduated with a PhD in biophysics in 1955. Ernest C. Pollard, a scholar of the physics of the living cell, was his mentor. The title of Caspar's dissertation was "The Radial Structure of Tobacco Mosaic Virus."

During the following years, he worked with such other great scientists as Max Delbrück, James D. Watson, Rosalind Franklin, and Aaron Klug at such leading laboratories as the California Institute of Technology, King's College and Birkbeck College in London, and the MRC Laboratory of Molecular Biology in Cambridge, England. In 1956, Caspar [2] and Franklin [3] published two separate papers, back-to-back, in *Nature,* demonstrating that the viral RNA was deep within the helical protein rod in the TMV virus. In 1958, Caspar initiated an important scientific hub for structural studies of macromolecules at the Children's Cancer Research Foundation at Boston Children's Hospital. In 1972, this laboratory moved to Brandeis University in Waltham, Massachusetts, and in 1994 to the Institute for Molecular Biophysics at Florida State University in Tallahassee, where he stayed for the rest of his career. This is where in 1996 my wife and I visited him and I recorded a long conversation with him from which excerpts are quoted below [4].

Recently, I discussed the value of observing general trends in establishing physical laws and the importance of detecting minute variations while reflecting on Erwin Chargaff's seminal discoveries concerning nucleic acids [5]. In this connection, I find it especially noteworthy that Caspar called attention to the specificities of biological systems where "The uniqueness of the individual may not exemplify the properties of the group" ([4], p 11). In more of his words ([4], p 11):

> In physics, the greatest concern is finding the underlying, unifying principle: abstracting out all the individuality, the differences among all sorts of systems to come down to some basic core. When I started in biology, I had a feeling that the use of such an approach would be constructive in understanding biological organization. Today I think it is only a crude first step. Maybe we do find some generalization that is helpful for our comparing and categorizing different systems, for example, the structural organization of different viruses. Almost all isometric virus particles have icosahedral symmetry. But when we come down to such a core, we realize that what appears interesting in biology is not the underlying principle but the individual properties.
> We may want to understand human behavior in general, but what is most intriguing is the behavior of the individual. The differences among the members of the population is what make life interesting. *The uniqueness of the individual may not exemplify the proper-*

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Fig. 1 (in 3 parts) Donald Caspar at Florida State University, Tallahassee, 1996 (photographs by I. Hargittai)

> *ties of the group*. There is some paradox here, and this makes biology so fascinating. (emphasis by me)

In 1962, Caspar and Klug reported their discovery of the icosahedral virus structures [6]. They acknowledged the influence of R. Buckminster Fuller on their investigation and the paper included an image of Fuller's geodesic dome in Montreal. They wrote: "The solution we have found … was, in fact, inspired by the geometrical principles applied by Buckminster Fuller in the construction of geodesic domes. The resemblance of the design of geodesic domes … to icosahedral viruses had attracted our attention at the time of the poliovirus work."

Later, in 1979, Caspar and his associates noted that their work on the structure of poliovirus, again, the resemblance of geodesic domes to icosahedral viruses, facilitated their discoveries, as the example of the polyoma virus shows (Fig. 2) [7]. A few years later, the naming of the C_{60} molecule and recognizing its truncated icosahedral shape was also inspired by Fuller's work and in particular by his Montreal geodesic dome [8]. Caspar and his colleagues utilized the principles of efficient design and this guided them toward the establishment of the virus structures. In his words ([4], p 56):

> Considering the structure of the virus shells in terms of these principles, we have found that with plausible assumptions on the degree of quasi-equivalence required, there is only one general way in which isodimensional shells may be constructed from a large number of identical protein sub-units, and this necessarily leads to icosahedral symmetry. Moreover, virus sub-units organized in this scheme would have the property of self-assembly into a shell of definite size. The basic assumption is that the shell is held together by the same type of bonds throughout, but that these bonds may be deformed in slightly different ways in the different, non-symmetry-related environments. *Molecular structures are not built to conform to exact mathematical concepts but, rather, to satisfy the condition that the system be in a minimum energy configuration*. (emphasis by me)

Caspar established the icosahedral symmetry for virus structures early in his career. It took then considerable additional effort to answer the question: Why icosahedral symmetry? It was a fortunate coincidence that Fuller visited Birkbeck College where Klug worked at the time and though not everyone there became interested in what Fuller had to say, Klug did. He recognized immediately the connection between Fuller's physical geometry and the virus structures. When Caspar started his work in Boston, he was building models of icosahedral viruses. He gained important insight in which he found Kenneth Snelson's tensegrity sculptures most instructive. Tensegrity refers to the integrity

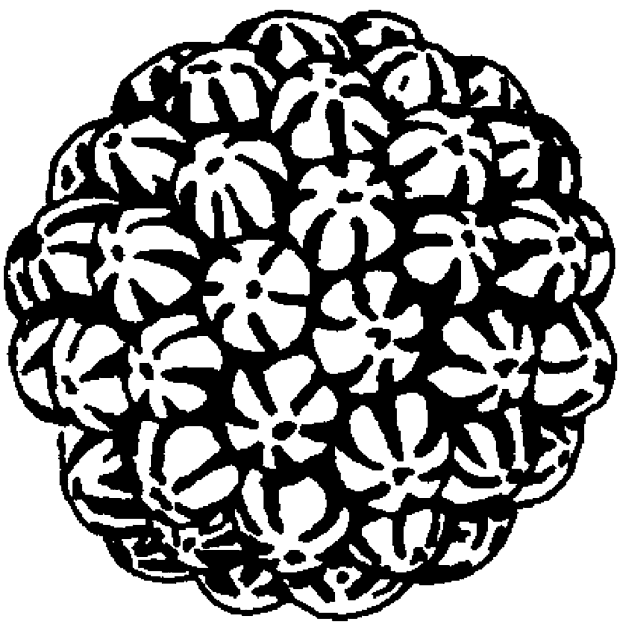

Fig. 2 Icosahedral polyoma virus drawn after [7]

of structures under tension. Fuller himself made good use of Snelson's ideas and constructions of tensegrity without necessarily giving credit to Snelson. Fuller was full of ideas, but it was never known what was his own invention or borrowed from others as he was not good in ascribing his sources. There was a close relationship, for example, between his considering space as physical reality rather than abstraction and the works of the medieval Italian architect, Francesco Borromini, but it is not known whether or not Fuller was acquainted with Borromini's work. Caspar met Fuller when Fuller was the Charles Eliot Norton Visiting Professor of Poetry at Harvard University in 1962. It was at the time when Caspar and Klug came up with the virus structure that was periodically perturbed. Caspar and Klug went out of their way to give proper credit to Fuller for what they had learned from him as seen in the quote above [6].

As for icosahedral symmetry, it is unusual. The most symmetrical arrangement for 12 spheres is "at the vertices of a regular icosahedron, which is the only regular polyhedron with 12 vertices. Thus, the icosahedral packing is the most symmetrical. However, it is not the densest packing. Also, it is not a crystallographic packing in terms of classical crystallography. When icosahedra are packed together they will not form a plane, but will gradually curve up and will eventually form a closed system" [9]. This is also illustrated in Fig. 2.

Above, I have already alluded to the connection between fullerene structures and the virus structures. Caspar took a broad view of icosahedral structures ([4], p 177): "A lot of related ideas about icosahedral structures have been around for a long time. Linus Pauling himself had recognized local icosahedral clustering in intermetallic compounds decades ago." Indeed, when shortly before his death, I asked Pauling in the fall of 1993 about why the chemical community appeared to be surprised by the discovery of buckminsterfullerene, he responded: "I am rather surprised that no one had predicted the stability of C_{60}. I might have done so, especially since I knew about the 60-atom structure with icosahedral symmetry, which occurs in intermetallic compounds. It seems to be difficult for people to formulate new ideas" [10].

Furthermore, on the connection with fullerene structures, in Caspar's words ([4], p 177): "Our theory for icosahedral virus design accounts very well for the design of the fullerenes. The basic geometry of hexamers and pentamers forming closed shells leads to icosahedral symmetry, which is the most regular way to do this. I had started to enumerate the less regular ways to create such structures, but it became a very tedious counting problem with very large numbers of possibilities. It was not until the higher fullerenes were discovered that the systematic enumeration of the non-icosahedral arrangements became a very worthwhile project."

Finally, Caspar spoke about quasicrystals with deep understanding. It was in 1996, at the time when it was still a long way to the general recognition of their correct interpretation ([4], p 177): "Quasicrystals are more interesting than the crystals in the traditional sense. In a quasicrystal the same atom may take different positions with equal probability. But even in a quasicrystal one can categorize the atomic motifs and their number is limited. These motifs with local pentagonal or icosahedral symmetry can be combined in many different ways to generate quasiperiodic lattices. The activation energy of switching from one arrangement to another though is probably very high. However, in the growth process, the different arrangements are of equal probability. Thus there is no way of predicting which way the atom is going to go, when the atoms are assembling."

If ever, today we can see the significance of Caspar's virus studies. His obituary in *Nature* stated [11]: "Donald Caspar defined the rules that govern the self-assembly of simple viruses. This laid the foundations for a new way of thinking about the molecular systems that regulate and drive all living cells. These rules made it straightforward to characterize other viruses, and then to design strategies to combat them. The same rules are also essential in designing viral vectors to deliver gene therapy."

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