

From Kuru to Nucleation, Aggregation, Polymerization and Crystallization in Biology and Medicine

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Nucleation is a word derived from nuclear family and refers to the concept of progenitor, the mother and the father of any family, which has been at the root of human life for many thousands of years. From it has emerged the concept of a breeding line of humans. Only in the last few centuries of civilization have physicists borrowed the word, and later biologists for Schwann's cell theory. Very recently it has passed to atomic theory, spectroscopy, radioactivity and to atomic bombs, fission and fusion. In physics any change in the free energy state of matter involves a nucleation or ordering of atoms into a new pattern as in any change to gas, liquid or solid or in the packing of atoms in carbon black, graphite, or diamond. Thus the word *nucleation* is not derived from atomic physics or cell biology. To be so deluded makes it difficult to understand the simple matter of pattern setting in any change of state.

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Molecular Casting

Infectious amyloid nucleants

We have repeated confirmation of resistance of a portion of infectivity of scrapie to temperatures as high as 600°C (Brown *et al.*, 2000). The

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enormous resistance to dry heat of a small fraction (about one part in 10^6) of infectious activity may represent a molecular casting, fingerprints of the nucleants.

Infectious nucleant or prion activity is the result of very close three-dimensional matching. Any particle which can sufficiently mimic the ability of the molecule to be nucleated to crystallize, to fibrilize, or to form a two-dimensional molecular sheet can trigger the process. Matching must surely be at atomic distances, close enough to evoke van der Waals forces and Coulombic forces, even H-bonding.

Can we preserve biological specificity of antibodies, antigens, pheromones, receptors, transmitters, ion channels and enzymes in organic molecular casts or atomic moulds?

The answer is yes, already for the first six items, and if we allow for synthetic hydrocarbon polymers for molecular casting, it may be so for enzymes.

Dermatoglyphic preserving of biological specificity

One of my adopted New Guinea sons has pointed out to me that a fingerprint using battery ink (MnO_2) is an example of such preservation with no atom of carbon and of biological specificity, more individual than the DNA sequence of identical twins.

Fossils show accurate speciation in paleobotany and paleozoology

Another of my adopted New Guinea sons has pointed out that fossil footprints allow for accurate classification and yet are not a source of DNA for speciation by polymer chain reactions. Nucleoli can be counted in inorganic fossils in cells extinct for millions of years.

Osmium shading in electron microscopy reveals details of molecular structure at nanometric distances

There is no contribution from carbon atoms to the image of an osmium or platinum shaded freeze-fracture electron microscopy photograph of individual molecules.

Mineral nucleants for crystal growth in outer space

McPherson and Shlichta (1988) sent a series of proteins into outer space to avoid the convection of fluids by the gravity of the Earth. They nucleated them with a selection of ground minerals. A subset of minerals usually initiated crystal formation in one or another of the proteins, a different set for each protein and differing forms of epitactic crystal growth for a given protein with each mineral.

What makes a diamond hold together?

Two polished ancient Chinese copper mirrors applied face-to-face stick together and require considerable force to separate them. A stack of newly opened clean microscopic cover slips slide one upon the other, yet it requires considerable force to separate them.

A diamond, the hardest of minerals, can scratch steel, yet it is still only made of carbon, the same as carbon black, coal or graphite.

Sulfur may be pure yet malleable, ductile, fragile or clay-like and of many colors depending how the S atoms are packed. Such is the nature of the van der Waals' forces that are brought into play at atomic distances.

Twinning of minerals

There are at least 200 twinning possibilities for quartz (SiO₂). Most possible forms have been found in the over 30 000 years of searching for them. When one new twin "form," "strain" or "species" is found, it is usually named for the region where it has been found. It is common to find

other examples of this particular “strain” of twinned quartz in mining shafts for many hundreds of kilometers around the first finding, yet nowhere else on Earth. Much the same is true for diamonds, emeralds and rubies, and for other examples of twinning in mineralogy.

Industrial viruses and “ice nine”

Kurt Vonnegut, Jr wrote of “ice nine” in his book *Cat’s Cradle* (1963): a fictional approach to the problem of nucleation based on a sound understanding of the phenomenon. His brother, William, was a major meteorologist fully familiar with non-DNA or non-RNA containing viruses and the World War II ethylene diamine tartrate problem of the industrial viruses, which nucleated the slow appearance of bubbles of large crystals of the compound made for optical purposes. Kurt Vonnegut, Jr. got the idea right.

Amyloid enhancing factors are scrapie infectious amyloid nucleants

For some 35 years, I have been aware of the work of amyloidologists in their attempts to accelerate the appearance on AA amyloid deposits in animals primed with inoculation of AgNO₃ or heterologous casein. Their discovery of amyloid enhancing factors, which were active in high dilutions and difficult to purify, remind me of our problems with the infectious agents of scrapie or kuru. I suggested that amyloid enhancing factors were scrapie-like agents (Gajdusek, 1977, 1988, 1991, 1994a, 1994b; Niewold *et al.*, 1987).

Any β -pleated polymeric assembly as a two-dimensional sheet or as a fibril may act as a heteronucleant for different amyloidogenic proteins

Amyloid deposits in man or animals are always found to be contaminated with other proteins similarly polymerized into fibrils — even copolymerized. These are all the proteoglycans and glycosaminoglycans as well as



Fig. 1. A prepubertal Gimi boy of about ten with kuru who requires aid to remain standing. He shows the spastic strabismus which most children develop in kuru. He died a few months later in 1957 (DCG-57 NG-1150).

plasma P-protein, chymotrypsin, ubiquitin, light chains of gamma-globins, and other amyloidogenic proteins.

Tropocollagen is nucleated to fibrilize not only by submicroscopic fibrils of tropocollagen but also by dimers and polymers of glycosaminoglycans or proteoglycans, and not by heparin which is a single-bonded dimer (Obrink, 1973).

Synthesis of prion-like infectious nucleants

Katarzyna Johan (Lundmark) and Per Westermark (1998) succeeded in getting *in vivo* heterologous nucleation of β -fibrillary protein polymerization into amyloid fibrils with synthetic amyloid enhancing factors. Such heterologous nucleants are synthetic peptides from the highly fibrillogenic

section of the amyloid precursor protein or both transthyretin and insulin associated amyloid. They serve to nucleate the fibrilization of the AA amyloid precursor protein when polymerized into small fibrils, but not as unpolymerized peptides. Labeling with I¹³¹ has served to locate AA amyloid fibrils that have been nucleated by these heterologous amyloid-enhancing factors. Thus, if these replicating systems are thought of as being alive, they have already synthesized “life” and published their findings.

Per Westermark and his colleagues have demonstrated the induction of AA amyloidosis by nucleation with heteronucleants such as silk and spider webs and by oral *paté de fois* in transgenic mice (Johan *et al.*, 1998; Solomon *et al.*, 2007).

Biological macromolecules all interact strongly with SiO₂, the most common solid mineral on the surface of Earth. Montmorillonite clay deposits cause delayed neurodegenerative diseases

Iler (1977) and Weiss (1981) have shown how silicon and oxygen in the form of SiO₂ can interact and bond to biological macromolecules or polymers in long series of strong attractions, whether they are carbohydrates, proteins, nucleic acids or fats. Silicon and oxygen are the two most common elements on the surface of Earth. The role of silicon is fully discussed in the Nobel Foundation's *The Biochemistry of Silicon and Related Problems*, in which Iler's article appeared. Thus binding to solids is the most likely origin of life, not a primordial oceanic liquid.

The high incidence foci of two very different diseases, Guamanian amyotrophic lateral sclerosis (*lytico*) and Parkinsonism dementia (*bodig*), of the Chamoro people on Guam, also occurred in the few remote inland villages of Honshu Island in Japan and among the Auyu and Jakai people around Bade and Kepi in southern West New Guinea (Gajdusek, Salazar, 1987). It has virtually disappeared from all of these places with the introduction of civilization. These three foci were restricted to remote communities in which a depletion of calcium produced a chronic severe deficiency of calcium in the diet, such that calcium sparing resulted in soft tissue deposition of calcium-aluminum-silicon,

or montmorillonite clay deposits within brain cells — along with heavy elements as the diet provided. These lay dormant for decades until triggered later in life causing specific neuronal damage that led to either *lytico* or *bodig*.

Nucleation is speleology

In exploring caves speleologists are familiar with nearly identical formations surrounding a fallen and shattered stalagmite or stalactite — very much like the rings of small mushrooms around an old large mushroom on the forest floor or the ring of young sequoia saplings around an old dead tree trunk. They often resemble even the odd idiosyncrasies in the parent formation.

At times a cavern of brown “toadstools” or one of the pink “phallic” organ-pipe cactuses is filled with dozens or hundreds of uncannily similar replicas. Then, several galleries below the dark brown “toadstools” in a gallery of pink “phalluses” stands a dark brown toadstool from nucleant which has tumbled down millions of years ago to the lower gallery from the “toadstools” above.

Nucleation in extragalactic space

The odd patterns of distant galaxies of billions of stars are well-known to all amateur astronomers who have viewed in awe the thousands of photographs we now have of them. They are by no means random patterns of stars, but lend themselves rather easily to classification according to similarities in appearance, as do most patterns in geophysics. These similar patterns appear in groups or in a very small fraction of the 2π steradians of space around us. The nucleation of such patterns across distances of huge numbers of light years is certainly cause for wonder.

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