ment progresses it becomes more and more difficult to get the drug dosage within acceptable limits: too low, and rigidity occurs; too high, and dyskinesia, distressing writhing movements, results. Consistent therapy eventually becomes impossible. Some authorities say the deterioration simply reflects progressive degeneration of the nigra. Others contend it is due, in part at least, to a toxic effect of the L-dopa itself. Long-term regimes with MPTP-induced parkinsonian monkeys, some treated with L-dopa, some not, should give important data on what really is happening.

The question to be resolved now, of course, is whether or not MPTP has anything at all to do with the natural disease. The unfolding story of MPTP happened to coincide with the accumulation of as many as 80 twin pairs in several studies relating to the genetic component of the disease. The answer seems to be fairly clear: "for most patients genetic factors are not important," wrote Langston and Donald Calne, of the University of British Columbia, in a recent review. "We conclude that environmental factors are likely to play a part in the etiology of Parkinson's disease in most patients."

Langston notes that most major neurological diseases can be identified from descriptions of symptoms in literature going back to the Bible and beyond. Not so for Parkinson's disease. "There doesn't seem to be any recognition of it before James Parkinson's description in 1817, so perhaps it is related to the advent of industrial society." Irwin notes that MPTP can be synthesized from a mixture of very simple chemicals and under very mild conditions. Incidental synthesis at low levels during other processes is therefore conceivable. He and Langston plan to look for traces of the chemical in autopsy specimens of Parkinson's patients.

The very high selectivity of the neurotoxicity is a puzzle and a challenge. The cells of the substantia nigra are not the only ones in the brain to produce dopamine, and yet this group is the only one affected in the disease. Substantia nigra cells have high levels of the black pigment neuromelanin, but then so do other cells that are spared. What is special about the substantia nigra?

These cells produce large amounts of dopamine, which are pumped up processes, released onto striatum cells, and then taken up again. This secretion/reuptake cycle in the striatum might well intensify the dopamine association, thus making a quantitative difference between the cells of the substantia nigra and other dopaminergic brain centers. The adrenal medulla also makes dopamine, but in this case as an intermediate in the synthesis of epinephrine. The adrenal medulla is also unaffected by MPTP.

Langston and his colleagues have recently been looking at the metabolism of MPTP in the hope of pinning down its toxicity. First, they noted the removal of the double bond in the pyridine ring makes the product completely innocuous, thus indicating that oxidation in this ring might be important in the toxicity. Indeed, it turns out that MPTP is very rapidly oxidized to the 1-methyl-4-phenylpyridinium ion (MPP+). Langston and Irwin suspect that MPP+ itself is not the toxin they seek but that the culprit lies somewhere in between it and MPTP.

Blockage of the MPTP to MPP+ oxidation in a test animal, by pretreatment with a monoamine oxidase inhibitor, prevents the development of the condition. As it happens, monoamine oxidase inhibitors are used in Europe, but not in the United States, in the treatment of Parkinson's disease. "The fact that here we have come across a drug that blocks MPTP neurotoxicity and is used in treatment of Parkinson's is of more than passing interest," notes Langston.

Progress has been like dismantling a Chinese puzzle, says Langston: "Every step forward we make we seem to push the problem back a step. We've found the metabolite, and we've found out how to block the metabolite and so prevent the disease. We seem to know more, but we still have no idea why the nigral cells are specifically affected."

—ROGER LEWIN

Crystal Anisotropy Directs Solidification

Simplified mathematical models of solidification elevate crystalline anisotropy to main player in selecting dendritic growth patterns

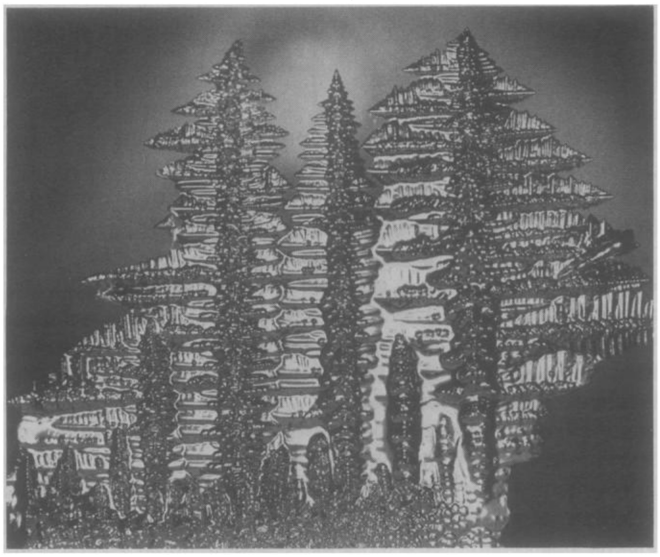
Two groups of theoretical physicists have produced evidence for the essential role of crystalline anisotropy in determining the feathery dendritic growth patterns assumed by many materials in growing from the melt or vapor. "You need to have anisotropy to get the side branching characteristic of dendritic growth," says Eshel Ben-Jacob of the Institute for Theoretical Physics at the University of California at Santa Barbara, a member of one of the groups.

No one who has marveled at the intricacies of snowflakes, whose hexagonal patterns reflect the symmetry of ice crystals, would be surprised at the findings. Nonetheless, previous work had declined to treat anisotropy effects, partly because the problem was fierce enough without them. Because of the simplified nature of the mathematical models used by the theorists, however, some researchers wonder if they are realistic enough for the asserted role of anisotropy to be accepted without further study.

Not all solids exhibit dendritic growth. Consider a molten, elemental metal encased in a container that is maintained at a temperature just below the melting temperature. Solid will freeze out on the walls of the container and grow smoothly inward at a rate limited by how fast heat can flow from the hot liquid through the solid to the container walls.

If, however, for some reason such as the presence of a seed crystal, solid forms initially in the center of liquid, it will grow outward toward the cool walls through liquid that has cooled to below the melting temperature. Growth into an undercooled liquid of this type is unstable. Small bumps or perturbations on the surface of the solidifying material grow faster than neighboring areas, forming fingers of solid that project into the liquid. Later, perturbations on the fingers result in side branches and so on. Eventually, the feathery dendritic patterns exemplified so well by snowflakes result.

Economically important instances of dendritic growth occur in multicomponent metal and semiconductor systems even when growth is not into an undercooled liquid. Here chemical diffusion of minority components plays a role analogous to heat diffusion and leads to dendritic growth, which is undesirable. For



Dendrites

Tin solidified from the melt exhibits typical dendritic growth patterns. [Photograph: Kurt Nassau, Western Electric]

example, dendrite formation can deleteriously effect the mechanical properties of metal alloy castings.

The two groups of theorists considered the simplest case, that of a single component material solidifying in an undercooled liquid. As the liquid solidifies, latent heat is released that must diffuse through the liquid to the cool container walls before growth can continue. The problem comprises a second order partial differential equation that describes the thermal diffusion and two boundary conditions. One condition requires that the rate of heat production at the interface equal the rate at which heat diffuses away. The other fixes the temperature at the interface in terms of physical properties of the system, such as the melting temperature.

Because the interface moves with time, the problem is a nonlinear one that has stoutly resisted decades of attempts to solve it. In the early 1960's, groups in the Soviet Union and the United States independently found solutions for part of the problem. American researchers now speak of the Mullins-Sekerka instability, after William Mullins and Robert Sekerka of Carnegie-Mellon University, who initially considered the case where the motion of the interface was slow enough to be neglected.

Using a technique called linear stability analysis, in which deviations from the smooth interface are introduced as small perturbations, Mullins and Sekerka verified that spherical interfaces are unstable. There are two effects. The destabilizing one occurs because the temperature gradient in front of a perturbation projecting into the liquid is slightly higher than that ahead of the smooth part of the interface. There is a positive feedback effect in which the higher temperature gradient enhances thermal diffusion, which causes more growth, which increases the temperature gradient, and so on. Surface tension, however, acts as a counterbalancing force that stabilizes but does not eliminate the growing perturbation.

Surface tension acts to reduce the local melting temperature at the interface between solid and liquid. The surface tension is largest at the tip of the growing perturbations, so the reduction is greatest there. The lower melting temperature stabilizes the liquid against solidification and thereby slows the growth rate of the tip relative to other locations on the interface. The heat released from the growing, flatter parts of the interface also retards tip growth by diffusing toward the tip.

Competition between opposing forces that results in a unique physical property, such as the velocity of the tip of a growing finger of solid in an undercooled liquid, is one instance of a more general phenomenon that practitioners of nonlinear dynamics call pattern selection. Analogous problems occur in widely varying physical, chemical, and biological systems governed by nonlinear equations. The interaction of oil and water in underground reservoirs during oil recovery operations is a good example.

For dendritic growth, needle-shaped solids are a better starting point than planes or spheres. Unfortunately, the mathematics is less tractable, and only the problem with vanishing surface tension has been solved. The growing solid assumes the shape of a parabola (in the two-dimensional problem). The tip of the parabola is characterized by a radius and a velocity whose product is constant.

An unresolved issue stems from the fact that the mathematics allows any tip radius and velocity whose product equals the constant; that is, there is a family of allowed solutions. Experimentally, however, only one is chosen.

Parabolas are subject to the same Mullins-Sekerka instability as the planar and spherical interface. In particular, perturbations near the tip can grow into parabolic side branches on the main parabola. The main parabola is said to be "stable" if it maintains its shape near the tip and continues to grow while side branches periodically appear and then grow away from the tip.

As it happens, none of the parabolas is stable in this sense. But in the late 1970's, James Langer (now at the Institute for Theoretical Physics) and Heiner Müller-Krumbhaar (now at the Kernforschungsanlage Jülich in West Germany) of Carnegie-Mellon reconsidered the growth problem with surface tension included.

Using linear stability analysis, Langer and Müller-Krumbhaar showed that the addition of surface tension stabilized all growing parabolas if their tip velocities were above a certain minimum. They further proposed a "marginal stability hypothesis" in which the parabola selected in the solidification process was in fact the one with the lowest stable velocity. Experiments seem to support the hypothesis, but there has never been a proof. In particular, both analytical and numerical calculations of the tip velocity and side branch spacings have eluded researchers.

An important feature of the solidification problem is the fact that the temperature gradient in front of any part of the interface is controlled by the diffusion of heat from *all* locations on the interface, not just that part of interface nearest by. Theorist call the problem "nonlocal" for this reason. A "local" problem would be considerably easier to solve.

The two groups of theorists now touting the role of crystalline anisotropy have taken the tack of converting the complicated nonlocal problem into a local one in the hopes that the governing principles of the solidification process would be retained and more easily identified in the simplified model.

One group, consisting of Ben-Jacob, Nigel Goldenfeld, Langer, and Gerd Schön of the Institute for Theoretical Physics, constructed a boundary layer model as an approximation of the full problem. The second group, comprising Richard Brower (now at the University of California at Santa Cruz), David Kessler (now at Rutgers University), and Joel Koplik and Levine of Schlumberger-Doll Research Ridgefield, Connecticut, took what they call a geometrical approach. In essence, both groups find that growing dendrites do not form even with surface tension incorporated unless an anisotropy is added as well.

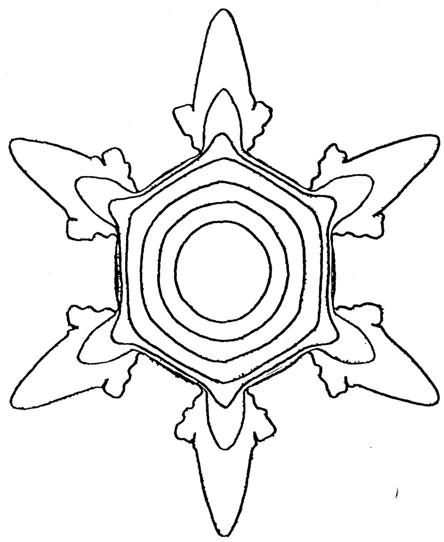
The boundary layer model devised by the theorists at Santa Barbara is the more realistic of the two in that it was derived from the full solidification problem. Boundary layer refers to the approximation that the liquid heated by the latent heat of solidification remains confined to a thin layer near the interface. The thickness of the boundary layer becomes a variable of time and of position on the interface. An equation governing the local boundary layer thickness replaces the diffusion equation of the full solidification problem.

In the real world, the temperature only gradually decreases to that of the container walls. For a large undercooling, however, most of the temperature decrease will be near the interface, and the approximation is rather good. Unfortunately, careful experiments are possible only for small undercooling. Ben-Jacob argues that "the important point is that the model retains all the physics of the solidification problem. For small undercoolings we won't reproduce all the experimental details."

For the simplest case of no surface tension, the boundary layer model does reproduce the parabolic solutions of the corresponding full solidification problem. In this respect, it is more realistic than the geometric model, whose zero surface tension solutions are not parabolas. Upon adding in surface tension, the theorists found nondendritic structures with bulbous tips, which is apparently the result of an attempt to minimize surface area and thereby minimize surface energy. This result contradicts the linear stability analysis of Langer and Müller-Krumbhaar, which predicted stable growth without anisotropy.

To introduce anisotropy into the problem, the Santa Barbara group added a new term to the equation fixing the interface temperature. The idea is that the motion of the interface between solid and liquid reflects the lack of thermal equilibrium there. In particular, the interface moves faster the more the interface temperature is depressed. A simple approximation is to make the depression linear with velocity. Anisotropy comes in by making the coefficient of the velocity vary periodically around the initial circular solid. Metallurgists know interfaces have anisotropic properties, so the idea is not arbitrary.

With this change in the model, the theorists were able to obtain rather realistic-looking dendritic structures (see figure). Ben-Jacob notes that the same tip velocity and pattern of side branches is obtained even for runs with different starting conditions; that is, the pattern selected is determined by the equations. This behavior is consistent with the marginal stability hypothesis, in which the tip velocity selection is seen as a dynamical effect. "It looks as if the marginal stability hypothesis is holding up," adds Langer.



"Snowflake"

Numerical simulation of the time evolution of dendritic growth in two dimensions with a sixfold symmetry imposed. The figure shows early and mid stages in the growth pattern. Calculation of later stages is precluded by the onset of long-range effects not included in the model. A real snowflake grows from the vapor, which is a problem with different physics than growth from the liquid, so it is not quite true that the mystery of snowflakes has been solved. [Source: E. Ben-Jacob, Institute for Theoretical Physics]

The geometrical model is a bit more controversial. Work on it proceeded in parallel at Santa Barbara and at Schlumberger-Doll when Langer was consulting there. However, when the Santa Barbara group was unable to obtain dendritic behavior from its geometrical model, it turned to the boundary layer approach.

In the geometrical model, the theorists devised an equation governing the normal velocity of the interface at each point in terms of functions of the local interface curvature (inverse of the radius) and its derivatives. Choice of the terms was determined mainly by general considerations of restrictions on growing interfaces. For example, there is no constant term because an absolutely flat interface will not move in a purely geometrical model. But there is a term proportional to the curvature because of the well-studied asymptotic result that an almost flat interface grows linearly with the curvature. The final equation has linear, quadratic, and cubic terms plus a surface tension-related second derivative but no nonequilibrium term.

The main objection to the geometric model is that the physics content is minimal. The coefficients of the terms cannot be quantitatively related to real physical properties for example. Levine admits this, but says "We tried to get the simplest set of equations that would give dendritic growth."

At first, dendritic behavior did not fall out when the equation was solved numerically. For example, in the two-dimensional case starting from a circular solid, mushroom-shaped structures inevitably resulted, whatever the starting conditions. This unstable behavior is called "tip splitting," because side branches forming at the tip dominate and the tip velocity plummets to zero. Real dendrites do not exhibit tip splitting.

It was only when the the tip velocity was forced to have an angular dependence similar to that in the boundary layer model that stable dendrite-like structures "grew." Moreover, the amplitude of this anisotropy had to exceed a critical value. Finally, in consonance with earlier ideas, the tip velocity of stable dendrites oscillates between high values during rapid growth and low values during side branch formation. And, as in the boundary layer model, for a given set of growth conditions, there is only one "average" tip velocity that is selected.

Have the two groups of theorists succeeded in keeping all the relevant physics of solidification in their simplified models? In one way, they certainly have not, as everyone agrees. Real dendrites do not have neighboring side branches growing into the same space. Local models cannot prevent this from happening, as there is no way for the tip of one side branch to know about a side branch approaching from some distance away.

Speaking of the local models, Sekerka at Carnegie-Mellon agrees that one has to put in anisotropy to get dendritic-looking structures. However, "anisotropy is a controversial point," says Sekerka. He regards it as yet to be proven that one could not get similar structures from the full solidification equations with only isotropic terms. The long-range effect that prevents side branch overlap, for example, could impose a pattern on the growing structure.

If the numerical simulations do not guarantee that the patterns seen in real dendrites are due to anisotropy and not long-range or other effects, it nonetheless looks as if physicists and metallurgists have good cause to take a deeper look at the possible role of crystalline anisotropy.—**Arthur L. Robinson**