

gen, and/or oxygen, are combined to form short covalent bonds. In the second, elements with very high densities of valence electrons are included to ensure that the materials resist being squeezed together.

The first approach gained favor in the late 1980s, when calculations suggested that the hypothetical compound  $C_3N_4$  may be even less compressible than diamond (4). However, after years of experiments, further calculations indicated that even for the least compressible  $C_3N_4$  structure, the shear modulus would only be 60% of the diamond value (5). New forms of carbon, including fullerenes and nanotubes, generated great excitement in the 1990s, when high-pressure processing produced very hard substances (1). However, these substances, which fall under the rubric of diamondlike coatings, can approach but never reach the hardness of diamond (6); furthermore, squeezing fullerenes and nanotubes is unlikely to be an inexpensive, practical synthetic route to diamondlike carbon. Three-dimensional boron-rich compounds, including  $B_4C$ ,  $B_6O$ , their solid solutions, and B/C/N phases, are very hard materials that deserve continued study. However, this approach is unlikely to produce materials with hardnesses exceeding those of boron nitride/diamond solid solutions, which are intermediate in hardness between diamond and cubic boron nitride (1, 2, 7).

In the second approach, transition metals that have a high bulk modulus but low hardness are combined with small, covalent bond-forming atoms such as boron, carbon, nitrogen, and/or oxygen. In this way, a material that can maintain both volume and shape can be created. This idea has led to highly incompressible phases such as  $RuO_2$  (8), WC, and  $Co_6W_6C$  (9). Unfortunately, these materials do not even approach the hardness of cubic boron nitride, owing to the partially ionic character of the Ru-O bond and the metallic nature of the W-W and Co-W interactions (3). Borides may be a better choice to achieve the required covalent bonding. Transition metal borides such as the tungsten borides  $WB_4$ ,  $WB_2$ , and WB are promising (1, 2). Elements with a higher density of valence electrons (and thus high bulk modulus) such as rhenium, osmium, and iridium also have the potential to form very hard borides (10); mixed-metal borides could be even harder (see the figure).

Once the best combination of elements is found, hardness could be increased by controlling the underlying nanostructure. For example, if the motion of dislocations in a material is hindered, hardness can be increased. This phenomenon is well known to occur in an ultrafine-grained diamond called carbonado (11). More recently, nanoceramics with a grain size of  $\sim 10$  nm have exhibited the same phenomenon (12). Superlattices of TiN/AlN or carbon nitride/TiN with a peri-

odicity of 6 to 8 nm also exhibit hardnesses two to three times as great as that of the bulk crystalline form of these materials (13, 14). In all these materials, the interfaces between the nanometer-scale components act as barriers to the movement of dislocations.

Despite all the research activity into synthesizing superhard materials, many opportunities remain unexplored. For example, the lightest element that could produce three-dimensional structures, beryllium, has been neglected, perhaps because it is toxic and may require specialized high-pressure equipment. Ternary phases of beryllium with other light elements—boron, carbon, nitrogen, and oxygen—could have exciting properties in their own right or in combination with high-valence electron density metals.

Despite their potential, new materials are unlikely to replace diamond altogether, because in addition to its hardness, diamond possesses many other amazing properties. It is the most incompressible material, has one of the highest indices of refraction, and has a room-temperature thermal conductivity five times as large as that of the best metals. The scientific challenge of finding a superhard

material that surpasses diamond in any of these properties will keep the field energized for years to come. Combining high hardness with other properties, such as chemical inertness and low-cost synthesis, could quickly yield practical benefits, for example, by providing a replacement for cubic boron nitride for cutting and polishing steel.

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#### BIOMEDICINE

## Hamiltonian Medicine: Why the Social Lives of Pathogens Matter

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**B**rushing your teeth is an experiment in social evolution. Brushing mixes bacteria that were previously surrounded by their clonemates with unrelated bacteria from another part of your mouth. This mixing reduces the relatedness among adjacent bacteria, which can in turn affect their behavior and, ultimately, whether they harm you. This argument is at the center of recent work suggesting that the social behavior of pathogens may be important in understanding disease virulence and antibiotic resistance.

Only some pathogens are dangerous. Understanding what causes virulent pathogens to emerge is a priority for both biologists and physicians (1). A key factor affecting the evolution of virulence is the number of different pathogen strains that infect a host (2–4). It was first thought that the

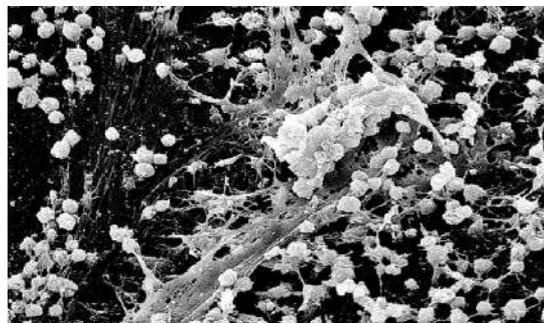
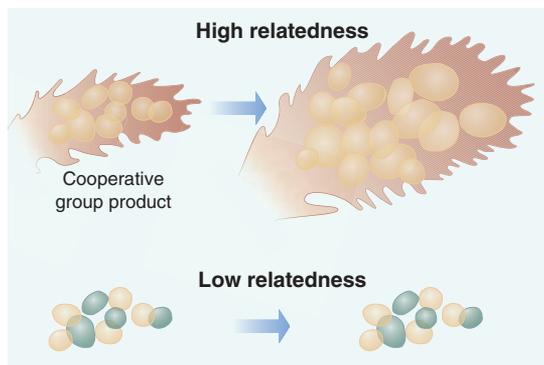
more strains there are in the host, the more virulent they should become. Frank (2) modeled the effect of multiple strains using Hamilton's kin selection theory (5). Originally developed to explain animal social behavior, kin selection theory revolutionized thinking by showing that related individuals cooperate with one another because of their shared genes (5). This approach can be applied to disease because multiple infections reduce relatedness among pathogens; kin selection then predicts that multiple infections should also decrease cooperation. The pathogens in Frank's model were not cooperating in a truly social sense but simply were solving the problem of how quickly to divide and reproduce. Frank predicted that low relatedness would make strains divide rapidly in competition, which would harm the host and increase virulence (2). Despite the elegant theory, many pathogens refused to cooperate with predictions. Studies on viral, bacterial, and plasmodial diseases found that mixed infection often favors the less virulent strain, showing that, contrary to Frank's theory, reduced relatedness often reduces virulence (3, 4, 6).

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This failure to cooperate with the theory is now being explained by the ability of related pathogens to cooperate with each other and to make use of shared products in their battle to overcome a host (see the figure) (4). For example, many bacteria collectively release feeding enzymes to break down host tissues, and the protein coats that protect viruses are shared, after manufacture, among all viruses in a cell. Shared products require cooperation because they can be exploited by selfish individuals who could use the product of others without making it themselves. Incorporating such products into Frank's model reverses the predictions: Lowered relatedness is now predicted to decrease virulence because it reduces the total amount of the virulence causing products (see the figure) (4). Griffin *et al.* (6) recently used the pathogenic bacterium *Pseudomonas aeruginosa* to test this hypothesis. *P. aeruginosa* infects almost any injured human tissue and is a problem in diseases such as cystic fibrosis, pneumonia, and meningitis. As is true for many pathogenic bacteria, growth of *P. aeruginosa* in vivo is limited by iron uptake because hosts actively withhold iron in order to combat infection. As a result, bacterial growth (and hence virulence) is linked to the cooperative release of iron-binding agents known as siderophores,

which scavenge iron and increase bacterial growth. In a wonderful verification of the theory, bacteria living with other highly related bacteria evolved to produce more siderophores than bacteria living with unrelated individuals (6). Bacterial cooperation can also increase virulence by reducing infighting (7, 8). Many bacteria kill nonclonemates with toxins known as bacteriocins, which reduce virulence by decreasing bacterial density. Interestingly, kin selection theory indicates that such chemical warfare is most likely to occur when the bacterial population has an intermediate level of relatedness (7). At high relatedness, there are too few nonclonemates to make the production of bacteriocins worthwhile; at low relatedness, each clone is too rare to significantly affect the other bacteria. Highest virulence, therefore, is predicted at either very high or very low levels of relatedness, owing to the low levels of bacteriocins. Massey *et al.* (8) simulated intermediate relatedness among bacteria by inoculating caterpillars with two species of bacteria that are known to harm each other with bacteriocins. As predicted, less harm came to



**The benefits of living among relatives.** (Upper panel) Highly related groups of pathogens (top) are better than low relatedness groups (bottom) at making shared group products—such as feeding enzymes, iron-scavenging siderophores, and protective slime. These facilitate growth and virulence or antibiotic resistance of the whole population. Dark and light ovals, two unrelated strains of bacteria. (Lower panel) Scanning electron micrograph of a *Staphylococcus* biofilm on medical equipment. The round objects are cells; a large amount of secreted slime is visible in the middle of the image. [Image: J. Carr, Centers for Disease Control and Prevention]

the caterpillars bearing mixed infections than to those with clonal infections. For this range of relatedness, therefore, the conclusions are the same as for the siderophore system: Lowering relatedness reduces virulence (8).

The concept of cooperation among pathogens is also emerging in studies of biofilms and antibiotic resistance. The idea that microbes spend their lives haplessly floating around has been superseded by the realization that they often live in highly organized biofilm communities attached to surfaces (see the figure) (9–11). Biofilms are involved in more than 60% of bacterial infections treated in the developed world and can contaminate almost any biological or industrial surface (9). The success of a biofilm depends on the production of slimy protective chemicals, a mix of polysaccharides, proteins, and nucleic acids. This collectively produced goop helps bacteria to adhere to surfaces, provides structural support, and can confer considerable protection from antibiotics (9,10). Slime production, therefore, is key to understanding the ecological success of biofilms. A recent simulation showed that biofilm formation was critically dependent

on high relatedness among the bacteria because slime, like siderophores, is a cooperative product (10). High relatedness also allows bacteria in biofilms to attain an optimal growth rate (10,11). With low relatedness, selfish competition is predicted to cause rapid and wasteful reproduction, which reduces the ultimate size and success of the biofilm (11). High relatedness may be common in biofilms if slime production reduces cell motility and thereby limits clonal mixing. Another interesting possibility is that low cell motility may itself evolve in order to raise relatedness and enable cooperation (11).

The recognition that pathogens can cooperate against us may greatly improve our understanding of disease. Nevertheless, many open questions remain. An important next step is to establish just how related pathogens usually are. Infections with multiple strains certainly occur, but particularly in biofilms there may still be high relatedness locally (9–11).

Is it typical for highly related pathogens to be more harmful? To date, high virulence has been associated with both low and high levels of relatedness (3) and, empirically, we know little about the relationship between relatedness and antibiotic resistance. Another question is whether, beyond the targeted killing by bacteriocins, pathogens can detect and respond to kinship in the short term. Finally, it is important to look at pathogen cooperation among species, because pathogens can exist in species-rich communities (10).

To recognize the growing significance of these ideas, we might view them as a distinct subset of Darwinian medicine (12) known as “Hamiltonian medicine” to reflect W. D. Hamilton's seminal contribution to social evolution (5). The implications are clear: Medical strategies that alter relatedness among pathogens can affect both virulence and antibiotic resistance. When next brushing your teeth, consider that you may be suppressing plaque by making your bacteria fight each other instead of you.

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