pliability of the 3D matrix was detrimental to the formation of adhesions that could activate specific signaling pathways. Thus, for adhesions to form properly and for activation of the correct intracellular pathways the 3D matrix must have the full complement of correct features: appropriate topography, molecular composition, and mechanical properties.

How do the properties of a cell-derived 3D matrix compare to those of substrates that induce focal and fibrillar adhesion formation? It is possible that each type of adhesion matrix (whether formed in vivo or in culture) has a unique combination of topography, molecular composition, and mechanical properties. Thus, focal adhesions are associated with a rigid substrate of limited molecular heterogeneity, whereas fibrillar adhesions attach to a matrix of soft, partly 3D fibronectin fibrils (see the figure). In contrast, 3D-matrix adhesions form with a matrix that is 3D, moderately pliable, and complex in its molecular composition.

The contribution of matrix properties to the formation of adhesions is poorly understood. Intuitively, one might think that the molecular composition of the matrix regulates the specific set of integrins and associated molecules recruited to the adhesion site. Pliability of the matrix may be crucial for regulating local tension applied at adhesion sites. This is consistent with the finding that local application of internal or external forces triggers the growth of adhesion sites and the assembly of bundles of actin filaments (stress fibers) (*5*). As the rigidity of the matrix increases, focal but not fibrillar adhesions are formed (*6*). Furthermore, adhesions are dynamic structures that are constantly being reorganized (*7*). A 3D matrix might be able to nucleate (seed) numerous small adhesions, inducing the formation of short actin bundles rather than arrays of large stress fibers.

Are all 3D matrices created equal? Probably not. In fact, it was shown long ago (*8*) that corneal endothelial cells and fibroblasts produce extracellular matrices that differ widely in structure and composition. It thus seems likely that matrices derived from different cells or tissues may each have a unique composition-topography-rigidity "signature" that determines their capacity to "sense" and to respond to the environment. It is noteworthy that certain adhesions formed in vivo resemble the focal adhesions of tissue culture and are associated with stress fibers (*9–12*). Returning to the question of whether adhesions formed in culture are physiological phenomena or merely "tissue-culture artifacts," Cuikerman and coworkers speculate convincingly that the focal and fibrillar adhesions formed in vitro may represent exaggerated precursors (to which I would add "variant forms") of the 3D-matrix adhesions formed in vivo. Their study supports a unified view of how the extracellular matrix exerts its effects on cell structure and fate, and highlights the importance of three-dimensionality, molecular composition, and pliability in this process.

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PERSPECTIVES: EPIDEMIOLOGY

Predicting the Unpredictable

Graham F. Medley

Disease predictions have reached epidemic proportions (*1–5*). Predicting the course of a disease in a population certainly fulfills a morbid fascination, but predictions that vary by two or three orders of magnitude are, for all intents and purposes, meaningless. Three papers published this week by *Science* (*1–3*) attempt to predict patterns of disease caused by the infectious agent responsible for bovine spongiform encephalopathy (BSE) in cattle and sheep, and its counterpart in humans called variant Creutzfeldt-Jakob disease (vCJD). To date, there have been 111 confirmed cases of vCJD in the UK. In their analyses of the UK vCJD epidemic, Huillard d'Aignaux *et al.* (page 1729) (*1*) and Valleron *et al.* (page 1726) (*2*) use statistical approaches to predict future numbers of cases. Both groups predict a long incubation period, with the numbers of predicted cases varying from several hundred (*2*) to hundreds of thousands (*1*). In their study of BSE in sheep, Kao and colleagues (*3*) "retrodict" the past epidemic, their principal interests being the extent to which this epidemic has increased human exposure to the BSE agent and its current prevalence in sheep. They predict fewer than 20 clinical cases of BSE in sheep this year (assuming a maternal transmission rate of 10%), but retrodiction of the peak number of infections varies between 25 and 25,000 (*3*). In each study, the width of the confidence intervals (or range of outcomes from different scenarios) can only be described as unhealthy. Why can't we do better?

In essence, the calculation is simple. The numbers of vCJD cases diagnosed during 2002 will be a convolution of the time of infection and the incubation period distribution (IPD), expressed as [(number infected in 1987) × (probability of progressing to disease during 15th year after infection)] + [(number infected in 1988) × (probability of progressing to disease during 14th year after infection)] + (etc.). Age, sex, and genetic predisposition to infection are among the factors that might complicate this relationship, but they do not change it.

Knowledge of any two of these three quantities (time of infection, IPD, and number of cases) allows the other to be estimated. For the current vCJD epidemic, we know neither the numbers infected nor the IPD in humans. In order to make predictions, one must be able to estimate these values simultaneously from case data, which is clearly impossible. For example, the current case data could have arisen from a small number of infections and a short IPD (predictions will be small) or a large number of infections and a long IPD (predictions will be large). Pick a prediction, and a suitable choice of infection rate and IPD will justify it. In contrast, accurate predictions of AIDS in the UK were possible because the pandemic was asynchronous. In that case, estimates of the IPD were available from cohort studies in which the time of infection of individuals was known or could be imputed, and infection times predated the UK epidemic [e.g. (*6*)].

Several approaches have been adopted to overcome these problems (*1, 2, 7*), but they require that strong assumptions be made. First, universally, the IPD is described as a parametric function. More cautious investigators have used extremely flexible functions (with large numbers of parameters) and have performed sensitivity analyses to extend the range of their predictions. However, any IPD estimate is conditional on the observed data, and the IPD is an (unsupported) extrapolation with no supporting data (*8*). Second, demography curtails the upper end of the prediction range: More than 5 million people have died in the UK since 1990 from non-vCJD causes, but some of them would have been infected.

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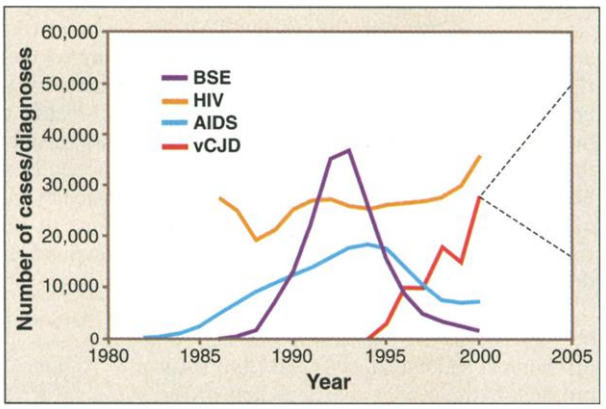
The longer the IPD, the greater the number of people with infections who would have died from other causes before progression to vCJD (*1*). Third, the investigators make use of the only other aspect of the case data: age (the mean age at death is 28 years). The distribution of ages is interesting; it appears constant with time. If the risk of infection and rate of progression were constant with age, then the age distribution should be increasing. However, it is impossible with current data to determine which of these aspects is age-dependent, and, again, inclusion of age effects can only be unsupported speculation. Finally, because all cases so far are of one particular genotype (which represents about 40% of the UK population), any predictions can only pertain to this subpopulation.



Life in a time of epidemics. Diagnoses in the UK (1980 to 2000): BSE (cases by year of confirmation), HIV (diagnoses per year × 10), AIDS (diagnoses per year × 10), and vCJD (diagnoses per year × 1000). The dotted lines show the range of predictions from (*1*) × 1000. Note that the upper 95% confidence limit is essentially exponential.

This situation contrasts with predictions of the recent foot and mouth disease (FMD) epidemic in the UK (*4, 5*), and the BSE epidemic in sheep (*3*). There are more data for these infections (largely derived from experimental infections), and, in the case of FMD, the IPD is well understood. The complications come in defining the infection function. Kao *et al.* (*3*) can predict with some accuracy the time period of the BSE epidemic in sheep (which is IPD dependent), but the predictions of the size (which depend on transmission) are very variable. Again, the lack of data is the source of uncertainty. However, even in the case of FMD, where data are abundant, it is probably wiser to stick with relative rather than absolute predictions of the effects of control measures.

There are several sensible approaches to solving these problems. The first is to ignore the unknown and treat epidemics as statistical processes (*9*). With this strategy only short-term predictions are reliable, and at the beginning of the epidemic the number of infected individuals is usually exponentially increasing. This approach does provide an upper bound to all predictions (see the figure).

The second approach is to extend and complicate the analysis by including additional information that reduces (rather than increases) variability. Present analyses of vCJD assume that the risk of infection is homogeneous, that is, all individuals are at equal risk (apart from the classifications of genetics and age). However, inclusion of risk heterogeneity can potentially reduce uncertainty in absolute predictions, as well as indicate relative incidence between groups. For example, under the (unproven but widely held) assumption that the BSE agent was transmitted by ingestion of infected food, individual variations in diet may be informative (*10, 11*). Similarly, rates of progression are known to increase with dose, so that heterogeneity in degree of exposure could also be informative (*12*). However, until risk factors for infection and progression are identified and the data exist to define their distribution in the general population, inclusion of heterogeneity in risk is unlikely to reduce uncertainty in prediction.

Consequently, predictions of the vCJD epidemic will continue to be plagued by wide confidence intervals. The current epidemic in the UK is a large cohort study: When the vCJD epidemic is over, we will perhaps have a good estimate of the IPD. If there is subsequently an epidemic in another population, we will have the data to enable more accurate predictions to be undertaken.

So are predictions worth the effort? I believe that they are, but not for the numerical values. Their intrinsic importance lies in developing an understanding of the processes underpinning these epidemics, and in providing an external validation of this understanding—if the predictions turn out to be wrong, we have to ask why. Valleron's qualitative prediction (*2*) that the age distribution will become bimodal is intriguing and more valuable than the number of predicted cases that they present. We should also watch how predictions change as case data are accumulated—encouragingly, each new prediction seems to have a lower upper bound.

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PERSPECTIVES: MATERIALS SCIENCE

Putting Metals into Polymers

Ian Manners

The valuable physical and chemical properties of many solids can be attributed to metallic elements. Examples include magnetic materials used in data storage, superconductors, electrochromic materials, and catalysts. It has long been recognized that incorporation of metal atoms into the one-dimensional chains of synthetic polymers may also lead to desirable properties. However, synthetic difficulties with creating macromolecular chains in which metal atoms act as a key structural component have slowed progress in the field (*1*).

Over the past decade or so, these synthetic difficulties have been overcome through the discovery of ring-opening polymerization and metal-catalyzed polycondensation methods. Substantial progress has been made toward the generation of hybrid metal/polymer materials with novel and useful properties (*1*, *2*). Self-assembly is emerging as a powerful tool to create supramolecular metal-containing polymeric structures. This approach helps to create self-organized, functional materials whose properties complement those of purely organic systems.

The first metal-containing polymers were materials with metallic substituents in polymer side chains (**1**) (see the first figure) (*3*). Related polymers with Os complexes attached to the polymer side chains (**2**) have recently attracted attention. Electron transfer between electrodes and the relatively inaccessible redox centers of enzymes can be slow, hindering electrochemical detection processes. Thin films of Os polymers can be used to mediate electron transfer or "wire" enzymes

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