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LETTERS

Gene Ownership

There has been recent media interest in commercial access to family material for genetic studies (Peter Aldhous, News & Comment, 18 Mar., p. 1552). This interest has arisen because of controversy surrounding an American biotechnology company's proposed exploitation of pedigrees and DNA from certain French diabetic families. The genetic information and material in question are currently held in France by scientists at the Centre d'Étude Polymorphisme Humain. The situation raises inevitable issues over who owns the rights to use specific families for genetic studies and who owns the rights to the genetic information arising from such studies.

It is easy and morally satisfying to dismiss these questions by saying that all the information arising from human genetic studies should be placed immediately in the public domain. This is not practical for several reasons, however, given the considerable investment in the Human Genome Project and commercial reality. Society urgently needs new medicines that address the pathology of diseases, rather than symptoms alone. Identification of genes involved in disease will lead to the validation of important therapeutic targets and more efficient drug discovery. New diagnostics, designed to identify individuals at risk for serious diseases, will enable patients to enter into frequent monitoring and early treatment programs. Preventive medicine, proved to be one of the most effective methods for reducing the devastating effects of serious disease, will become the treatment of choice in the future. The discovery of genes predisposing individuals to complex disorders will affect each of these areas enormously.

Making human genetic information freely available to all would not encourage biotechnology and pharmaceutical companies to use that information commercially. Unless a company can protect information and develop a proprietary position for its projects, it is difficult to justify the major financial commitment needed to turn discoveries into products.

Companies can protect information in several ways. The two most common ways are by patent protection or by trade secret. A third way used by both academic groups and by industry is that of lead time: whoever makes the discovery has time to capitalize on the information before anyone else learns of its existence. All these protection mechanisms are open to groups that do genetic research. There is considerable misunderstanding about the patenting of genes or gene fragments, and the situation remains largely unresolved. It seems likely that the opportunity to patent complete genes (as complementary DNAs) for direct use (for example, in a diagnostic kit or as a gene therapeutic) will remain. On the other hand, patent examiners have indicated that it is unlikely that random expressed sequence tags (or incomplete sequences) will be patentable until their utility has been defined. The situation regarding patent claims to genes (for example, coding for receptors) as a means for discovering small molecule mediators is similarly unclear.

There is no need to "own" families or DNA. There is, however, a clear need to protect the data derived from studies of those families—if necessary, by patents—to ensure proper and expeditious commercialization. The measure of the companies involved in disease gene hunting will be the speed and accuracy with which they uncover relevant genes rather than the ability to secure exclusive access to families and DNA.

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Antibiotic Resistance

For one who spends his time in the constant struggle to develop effective new chemotherapeutic agents, it was gratifying to see the attention that antibiotic resistance recently received in *Science* (15 Apr., pp. 360–393). However, I wish that the views of industrial researchers had been more fully represented, as a significant contribution to this field comes, either directly or indirectly, from the pharmaceutical industry.

In particular, the News Report by John Travis (15 Apr., p. 360) quotes remarks by James Knox that imply that full use is not being made of structural information that could be a basis for "rational drug design." This is not the case. Preclinical research groups at Roche use the latest techniques as well as the tried and tested methods of chemical variation around lead structures and microbial broth screening.

In 1990, a Roche research team at Basel published the three-dimensional structure

of a class C *beta*-lactamase (*1*), and several other *beta*-lactamase structures are used in our daily work. These enzymes are the frequent cause of high-level resistance to modern cephalosporins occurring in pathogens such as *Citrobacter freundii* and *Enterobacter cloacae*. Together with intensive enzymological studies (*2*), this structural work has led to potent "rationally designed" enzyme inhibitors, as has been disclosed in a recent patent (*3*). Current efforts at Roche and other companies are extending these molecular studies to the cell-wall biosynthetic enzymes that are the target of *beta*-lactam antibiotics (*4*). The structure of human dihydrofolate reductase was published by investigators at Roche (*5*), and in-depth investigation of the mechanism of bacterial resistance development is in progress (*6*). There are, however, many hurdles to be overcome before an effective inhibitor can become a successful antibiotic, and this takes time. The fact that, despite intensive research efforts, the progress is slower than desired indicates that the hurdles for a new agent, even if it is "only" an antibacterial, are high.

Rational design is only one line of attack that can be used. The recent discovery of cyclothialidine (*7*) by microbial broth screening with the use of a specific enzyme assay is another exciting development because of its new and unexploited target in the bacterial cell.

All in all, we are not relying only on the success of "old antibacterial drugs," but are looking to meet the challenge of emerging new and multiresistant pathogens with new medicines.

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In the justifiable concern of scientists, physicians, and public health officials about the alarming rise in antibiotic-resistant bacterial pathogens, with its potential for "medical disaster," a simple principle may have been overlooked. The processes of evolution and natural selection may be relied on to have produced wild-type bacterial populations that are exquisitely adapted for survival in the wild-type environment. The outgrowth of antibiotic-resistant strains results from these processes acting in an altered environment, namely, one containing the antibiotic in question. Acquisition of resistance requires the bacterium to synthesize new enzymes, to modify certain pump mechanisms, or to alter membrane permeability controls. These changes cannot be achieved without some biochemical cost, and the result is an organism that, while certainly at an advantage in the new antibiotic-containing environment, is no longer the specimen that was perfectly adapted to the wild-type environment. It may be predicted with some confidence then that returning the antibiotic-resistant form to the original environment will place it at some selective disadvantage in competition with the wild type, which will eventually replace it.

In practical terms this means withdrawing an antibiotic from use when the frequency of resistant organisms reaches an unacceptable level. After a suitable period, during which the incidence of the resistant form would fall because of competition with the wild type, the same antibiotic might again prove useful. The experience in Hungary (News Report, 15 April, p. 364) is consistent with this prediction, although appropriate studies would be required to demonstrate that the observed fall in antibiotic resistance was truly a consequence of reduced use of penicillin.

It is not hard to design on paper a system in which effective surveillance determines when an unacceptable level of resistance has been reached and, with the cooperation of physicians and pharmaceutical companies, the drug in question is withdrawn from use until the resistance level falls sufficiently. However, the combined effects of ignorance, economic interest, and political infighting, added to the inherent difficulty of mounting an effective surveillance operation (R. L. Berkelman *et al.*, 15 Apr., p. 368), would undoubtedly render implementation of such a system extremely difficult. At the very least, the population dynamics of resistant bacteria after antibiotic withdrawal should be studied to determine whether such a system would be of benefit.

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The continuing evolution of resistant strains of bacterial diseases has implications for health care, some of which are not immediately obvious. For example, let us assume that hospitals serve as a reservoir of resistant strains, which can be transported throughout a building before being detected. A reasonable assumption would be that

a hospital visit by a patient would result in a higher probability of infection by a resistant strain than would a visit to a physician's office. Because a disproportionate number of hospital emergency-room visits are from individuals without regular access to health care, infection with resistant strains of bacteria may occur disproportionately among those with the least resources to cope with them. Indeed, total population mortality from these resistant strains could easily be enhanced because of the reduced availability of health care available to these individuals after the hospital visit during which infection occurred.

Another reasonable assumption is that locations with a greater flow of patients would have a higher probability of maintaining a resistant strain. This implies that foci of infection could develop more readily before detection in multiphysician partnerships and clinics than in smaller clinics or those with a single physician. The dwindling number of single-physician practices therefore could have a significant epidemiologic impact on the spread of resistant strains.

Similar hypotheses can readily be tested from epidemiologic data on resistant strains and could have important public health consequences and provide further motivation for the expansion of infectious disease surveillance, as Ruth L. Berkelman *et al.* suggest (Policy Forum, 15 Apr., p. 368). It would be prudent at this stage for epidemiologists to ensure that observational designs are being developed to track these and other implications of antibiotic resistance.

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Statistical Medicine

With respect to the articles "Problems in clinical trials go far beyond misconduct" and "Ignorance is not bliss" by Rachel Nowak (Special News Report, 10 June, p. 1538), I agree with Richard Peto that "ignorance is the biggest form of misconduct," and it has been for *n* generations of doctors and others. Physicians often receive no training in conducting clinical trials, and the budding physician-cum-researcher is usually offered only *a* course in biostatistics "covering everything you ever wanted to know."

The symptoms are old, hence the patent medicine being offered (one good course for every doctor) is patently wrong. And the syndrome is worse than that because (i) there are long gaps between the course and the need for its lessons, and (ii) most statistics courses focus only on statistical analysis, not on how to collect good data in surveys, experiments, and clinical trials. Specialists in statistics are needed to guide the path to good data, and the doctors should be led to those paths.

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Corrections and Clarifications

In the Perspective by Donald G. York (8 July, p. 191), figure 1 was printed incorrectly. The correct figure and caption appear below.

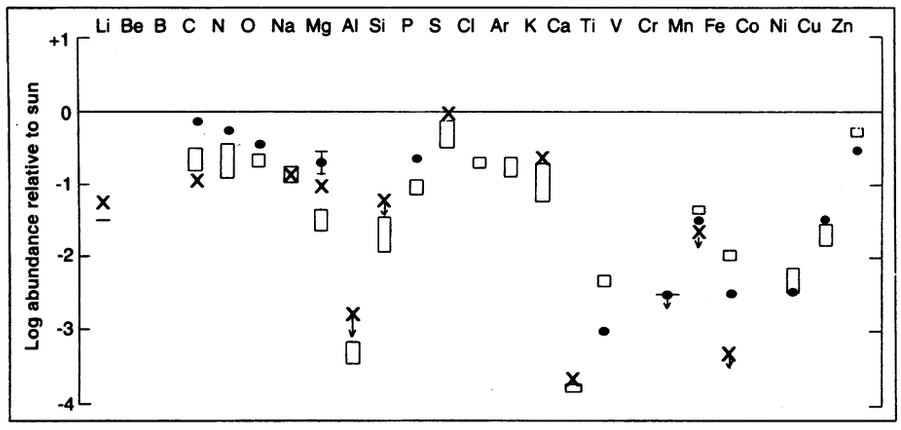

Fig. 1. Abundances compared to atomic number for the main dust cloud in the spectrum of ζ Oph. Open rectangles are from Copernicus data (*11*). Solid dots are new values from HST or high-resolution results from ground-based data (in the case of Ti II). The ×'s represent results from trace ionization stages (*12*), relative to neutral sulfur. Data for Na, Li, K, Al, and Ca, not covered by Cardelli's summary, are included.