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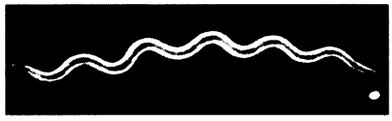

Serious concerns

Correspondents focus on test animals in a continuing discussion of how to assess risks from the many substances that must be tested for possible toxic effects to humans; an advocate of Lyme disease patient groups points to "mounting" evidence that the Lyme disease spirochete, *Borrelia burgdorferi* (above), can persist in some patients despite antibiotic treatment; and a representative of the American Academy of Actuaries speaks out on genetic discrimination.

Lyme Disease Research

The main focus of Eliot Marshall's article "Lyme disease: NIH gears up to test a hotly disputed theory" (News & Comment, 13 Oct., p. 228) is the controversy between patient advocacy groups and treating physicians on one side, and university-based researchers (who frequently dispute the existence of chronic Lyme disease) on the other. The article reports that the patient groups' tactics to have chronic Lyme disease studied "have angered research leaders such as Allen Steere of Tufts University." Is patient-initiated research really so bad?

Steere has been one of the most outspoken skeptics about the existence of a chronic Lyme disease epidemic (*1*) and one of the most outspoken proponents of the success of modest (10- to 30-day) courses of antibiotics (*1*). In 1993, Steere wrote (*2*) that, in Lyme disease, "Standard antibiotic treatment probably fails less often than one might think. Most apparent treatment failures actually reflect misdiagnosis."

However, evidence is mounting that the Lyme disease spirochete, *Borrelia burgdorferi*, can persist in some patients despite antibiotic therapy. The spirochete has been isolated from the skin (*3*, *4*), spinal fluid (*4*, *5*), blood (*6*), ligamentious tissue (*7*), and iris tissue (*8*) of patients after antibiotic therapy, including intravenous or long courses of supposedly curative antibiotics, or both (*9*).

It may surprise some to learn that in the first few years he was associated with Lyme disease, Steere promoted the idea that antibiotics were ineffective. In 1977 (*10*), Steere and his colleagues stated, "We remain skeptical that antibiotic therapy helps." In 1978, Steere and his colleagues wrote (*11*), "To sum up the therapy of Lyme arthritis (Lyme disease), it appears that at this point only symptomatic treatment is feasible." In a 1979 paper about the neurological abnormalities of Lyme disease (*12*), Steere and his colleagues reported that they "have noted no benefit from antibiotic treatment." However, an extensive literature search revealed 17 medical papers published before 1979 reporting the efficacy of antibiotics in treating Lyme disease. Only one (besides Steere's) reported no benefit.

The controlled studies (*12*) to see whether longer term antibiotics can help prevent chronic or relapsing Lyme disease (both successful) were performed in Europe. As Steere himself is quoted by Marshall as saying, the proposed National Institutes of Health study of chronic Lyme disease "would never have been funded" through the "normal mechanisms" of investigator-initiated research.

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■

Diet and Test Animals

Philip H. Abelson's editorial "Flaws in risk assessments," (13 Oct., p. 215) correctly points out the critical role that diet can play

in public health and the assessment of risk. He raises two important issues: (i) over the last two decades there has been a steady increase in variability, decrease in survival, and increase in degenerative diseases and tumor incidence, proportional to a concurrent increase in body weight, across a number of rodent species and strains used in toxicity testing; and (ii) relatively small differences in dietary intake, as reflected by body weight differences, can lead to significant changes in the way animals respond to chemical or agent exposure (*1*, *2*). We agree with these two observations, and wish to add three others based on our work in this area (*3*).

First, failure to control or stabilize body weight between and among control animals, by allowing ad libitum feeding, results in increased inter- and intra-experimental variability. Recent studies suggest that between 60 and 95% of the variability in the occurrence of liver tumors in different studies can be accounted for by differences in body weight (*3*, *4*). Other studies suggest that a similar relationship between body weight and other pathologies may also exist (*5*). Thus, the impact of body weight differences on the induction of chemical or agent toxicity can be as significant as test agent dose (*6*).

Second, according to a broad-based consensus developed over 50 years of work within the field of dietary restriction, it appears that, while individual dietary components may be of importance relative to the frequency of specific pathologies, total caloric content, rather than any one macro- or micronutrient, has the greatest overall impact on the health of the animal (*3*, *4*, *7*, *8*).

Third, dietary intake exerts its effect on a wide range of physiological, metabolic, and molecular parameters important to the toxicity of compounds (*1*, *9*). Many of these effects are observed in both sexes and across different genotypes and species, including monkeys and humans (*3*, *7*, *10*). Additionally, in certain cases, primary cell cultures in vitro can reflect the dietary history of the animal from which they were excised in their capacities for transformation, oncogene expression, or DNA repair (*3*, *10*, *11*). Failure to adjust for differences in dietary intake and the resultant differences in toxicity mechanisms will increase variability, reduce reproducibility, and possibly provide misleading information.

In the absence of malnutrition, generally, the lower the body weight, the greater is the ability of an animal to cope with chemical or agent exposure. Therefore, in optimizing the health of animals used in testing and research, one could potentially reduce body weight such that they become less sensitive or refractory to chemical- or agent-induced toxicity. It is important that the biological mechanisms involved in the initiation and expression of toxicity and carcinogenicity end points be functional and that the body weights of control and test groups be comparable. Scientists should therefore use moderate and reasonable dietary control measures in reaching the goals noted above. The Food and Drug Administration is currently preparing two documents for publication in the *Federal Register* which identify the problems associated with uncontrolled food consumption and address which levels of dietary control are appropriate to achieve standardized growth curves.

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Abelson states that changes in weight gain characteristics of rodents used in chemical toxicity and carcinogenicity studies affect the outcome of numerical risk assessments derived from these studies. While there are few published data on which to base an evaluation of this issue, this assumption is likely correct. The National Toxicology Program has performed rodent cancer assays on numerous substances of potential importance to public health. We have examined this issue over the last decade (*1*) and have come to appreciate the complexities associated with dietary restriction that are only hinted at by Abelson. The ad libitum offering of food to test animals was standard practice in the 1970s and remains so today. The inadvertent selection of faster growing rodents, combined with improved animal husbandry, has paradoxically resulted in shorter lived animals. Dietary restriction is known to lessen the incidence of "spontaneous" tumors in control animals, and to dramatically increase longevity. However, the effects of marked versus moderate dietary restriction on the sensitivity of the animal model to respond to a chemical carcinogen appear to differ, and at this point insufficient data have been collected to determine exactly how the response of the assay changes in relation to the degree of restriction. Because of this, the National Toxicology Program has taken a different approach. While continuing to offer food ad libitum, we have recently changed the diet to decrease the protein and increase the fiber content. We have also ensured that the breeding bias toward selection of faster growing rodents is stopped. Preliminary results indicate that these changes have resulted in slower rates of rodent growth in 2-year studies, and will decrease the incidence of Fischer rat nephropathy, which is a dietary protein-related disease responsible for early mortality. We believe that these changes will maintain the sensitivity of the rodent models to detect carcinogens and also stabilize the quantitative response of the assays with respect to time. It is important to note that the reproducibility of the results in a qualitative sense is not at issue here, as we and others have noted good reproducibility in replicate assays with regard to target organs and tumor types. However, Abelson's goal of "time invariant" reproducible quantitative results may be unattainable as unappreciated fluctuations occur in the rodent bioassay as in any biological system. It is unlikely that simply offering a restricted amount of food will prevent these fluctuations from occurring.

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Genetic Discrimination: Actuarial Aspects

As a policy spokesman for the actuarial profession, I would like to respond to the 20 October Policy Forum "Genetic discrimination and health insurance: An urgent need for reform" by Kathy L. Hudson *et al.* (p. 391). While the Policy Forum highlights certain theoretical concerns and proposes regulatory restrictions, the impact of genetic information on insurance rates and availability is in some cases exaggerated, and the impact of the restrictions on the voluntary insurance market, and on the risk classification system that is one of its essential elements, is largely ignored.

Actuaries have found that risk classification serves three primary purposes in the design of financial security systems: it promotes fairness, it permits economic incentives to operate and encourages widespread availability of coverage, and it protects the soundness of the financial security system. As a basic principle, any sound risk classification system should reflect cost-of-insurance differences based on relevant risk characteristics.

Clearly, individuals with certain genetic traits may have risk characteristics that would result in increased claim costs. The Policy Forum refers to the risk-sharing function of insurance. The main goal of insurance risk-sharing is to allow individuals subject to an unpredictable risk to pool resources, so that the individuals who, on a random basis, may suffer the effects of the insured event will receive the benefit of the pooling mechanism, which will in turn be appropriately paid for by other members of the class. If all the insured in a class face a roughly comparable probability of loss, they will be willing to pay a premium equal to their expectation of loss.

There is a great temptation to use insurance as a means of providing subsidies. Subsidies may, in some cases, be warranted; but trying to collect them through insurance tends to create incentives on the part of both the insured and insurers that warp the insurance mechanism, reduce the availability of coverage, and in some cases even threaten the soundness of the insurance system.

The Policy Forum suggests that genetic information is "distinct from other types of medical information" and suggests that the appropriate response to the availability of genetic information is to ban its use in the determination of health insurance rates and insurability, at least. Genetic information is often costly to obtain, and the benefits of reduced claim costs may not be commensurate with the cost of obtaining the information on the numerous applicants screened every day by insurance companies. Many genetic factors are related to long-term tendencies that are likely to result in an increased, but not unaffordable, rate—if the appropriate risk factors are used. Special situations, such as the reticence of persons to become involved in certain studies because of the fear of insurance restrictions, can probably be handled by special coverages or other techniques.