Letters

Reporting Biological Structures

The article "The missing crystallography data" by Marcia Barinaga (News & Comment, 15 Sept., p. 1179) draws attention to an important problem but does not mention that the problem is not limited to crystallography. It pervades all of biological structure work. A similar concern about the "missing NMR data" is emerging in the nuclear magnetic resonance community. More than 30 peptide and protein structures and an even larger number of oligonucleotide structures derived from NMR had been reported by the middle of 1988 (*1*), and new NMR structures are being published almost weekly. Yet for only one of these has the full set of data and complete detail of the analysis been made generally available, although more are promised. Even for the first protein NMR structure reported (*2*), one will find neither a definitive set of coordinates nor the definitive data set in the public domain.

In part this reflects the fact that the structural interpretation of NMR data is more problematic than that of x-ray data. It requires assumptions (specifically about the dynamics of the structure and the extent of indirect magnetization transfer) that are not easy to test and may or may not apply to the structure in question. Furthermore, it is becoming increasingly clear that the final structure is dependent on the method of data analysis (*3*), and it is by no means evident that a meaningful *single* set of atomic coordinates can be given for an NMR structure, even though the general topology of the molecule appears well defined. While remarkable success has been achieved in finding a rather precise correspondence between a crystal and an NMR structure, independently determined in the case of tendamistat (*4*), more recent work shows that the particular method of analysis does not necessarily give a complete set of structures compatible with the data (*5*). There is as yet no agreement in the field of the effectiveness of the different methods of refinement that have come into use (*6*), and the sources of error inherent in each have not been sufficiently studied.

These considerations make the placement of the complete sets of original NMR data for each published structure into the public domain that much more urgent. The work of Wüthrich and colleagues (*4*) sets a high standard of thoroughness in reporting that is rarely met. While the fear of being "scooped" (or disproved) at the data analysis step is to some degree understandable, such practices should be discouraged. Given the pitfalls of NMR data interpretation, nowhere is there as much need for independent verification of the proposed structures as there is in NMR. Fred Richards' dictum—"if you want to do a structure and sit on the data, fine, but don't publish it"—is an important safeguard against the proliferation of published structures based on little more than an overinterpretation of the data.

The International Society of Magnetic Resonance has established a commission under the chairmanship of G. C. K. Roberts (University of Leicester, United Kingdom) which should, in its forthcoming report, provide a set of guidelines as to what kind of documentation should be required before a structure is proposed. Until such standards are generally accepted and the proposed structures can be verified by independent groups using different methods of data analysis, we have no way of knowing whether a specific NMR structure is merely a plausible computer-generated sculpture or a scientifically valid and useful rendition of molecular reality.

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Electric and Magnetic Fields

Philip H. Abelson (Editorial, 21 July, p. 241) describes the Office of Technology Assessment (OTA) report (*1*) on possible health hazards of 60-hertz electric and magnetic fields.

But just what is the problem? Dozens of epidemiological studies have been reported. Some of these claim weak associations between occupational or residential exposure to fields and diverse illnesses. Because of the many ambiguities associated with these studies, the evidence is weak and inconsistent, and no firm conclusions can be drawn—as Abelson and the OTA report acknowledge.

Abelson mentions some reported biological effects of electric or magnetic fields. These effects are unconfirmed, associated with field levels far above those implicated by the epidemiological studies, have only speculative significance to human health, or all of the above. Not much evidence for a hazard there, either.

The possible hazards of power line fields have been under constant study for many years. The few proven hazards (for example, shocks from touching large conductive objects in strong electric fields) are obvious and easy to avoid. However, the bioeffects literature is filled with speculation and nonreproducible phenomena (*2*). The feeling is understandable that all this smoke implies that a flame exists, somewhere. That is insufficient reason to recommend "prudent avoidance" of fields. More research is needed, but it must be carefully targeted to reduce the confusion.

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"Psychic Stress" and Lung Cancer

In response to my letter of 10 March 1989 (p. 1255) Alvan R. Feinstein (10 March 1989, p. 1256) stated that his "remark about psychic stress, which Shapiro appears to have misunderstood, was intended not to refer to lung cancer, but to coronary disease. . . ."

I regret that Feinstein obliges me to quote him verbatim (*1*):

> The scientific validity of the data regarding smoking and lung cancer has long been regarded with suspicion because the investigators have failed to check two underlying sources of major bias that could have created the same distortions in both the trohoc and cohort studies. One such bias is in target detection. Because of cough, the smokers might be much more likely than non-coughing non-smokers to receive the X-ray, cytology, and other examination procedures needed to diagnose lung cancer. The other source of bias is in susceptibility. Although R. A. Fisher proposed that a constitutional (and possibly genetic) factor might lead to both smoking and lung cancer, a simpler common factor that can predispose to both smoking and reduced longevity is psychic stress, which has never received satisfactory investigation in the epidemiologic appraisals of smoking and its consequences.

In the same article, some 4500 words earlier, Feinstein refers to psychic stress as a possible risk factor for coronary disease. However, the reader should judge whether, in the above passage, Feinstein was referring to coronary disease or to lung cancer.

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Body Weight and Reproduction

Conclusions by J. E. Schneider and G. N. Wade (Reports, 16 June, p. 1326) about the control of reproduction of the Syrian hamster weighing 85 to 95 grams (3.0 to 3.3 ounces) when adult do not necessarily apply to women, as suggested in This Week in Science (16 June, p. 1231). For a woman weighing 57,000 grams (125 pounds) when adult 26 to 28% [16,000 grams (35 pounds)] is fat (*1*). Contrary to the conclusion by Schneider and Wade from the hamster data that "reproduction is controlled by the general availability of metabolic fuels, rather than by any dimension of body size," a large amount of data for women indicates that body size and composition are important to successful female reproduction (*2–7*). Fatter girls have menarche earlier than do thinner girls (*2, 8*). Menarche is delayed in very lean girls, sometimes to as late as ages 18 to 21 (*9*). Fatter women have a later age of menopause than do thinner women (*10*). Most important for fertility, it is well documented that when a woman loses 10 to 15% of her normal body weight, which is equivalent to a loss of one-third of her body fat, menstrual cycles and ovulation cease due to hypothalamic dysfunction (*2-7, 11*): the pulsatile release of gonadotropin releasing hormone (GNRH) becomes abnormal (*5, 6, 11*). The disruption is reversible: gain of weight restores normal GNRH pulsatile secretion, and thus fertility (*6*).

That a dimension of body size is important to the sexual maturity of women would be expected, since the survival of the human infant is correlated with birth weight; and birth weight is correlated with the prepregnancy weight of the mother and independently with her weight gain during pregnancy (*12*). Also, the caloric cost of a human pregnancy is about 50,000 calories, and lactation requires about 500 to 1000 calories a day. The main function of the 16,000 grams of stored female fat, equivalent to 144,000 calories, may be to provide energy for a pregnancy and for lactation (*2–4*). In prehistoric times, when the food supply was scarce or fluctuated seasonally, stored fat would have been necessary for successful reproduction, as Schneider and Wade recognize. Excessive fatness also disrupts reproductive ability in women, as it does in animals (*13*). Weight loss to the normal range results in the restoration of fertility.

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Response: The well-known correlation between fertility and body fat content has been heuristically valuable to many investigators, including us. We found the same correlation in Syrian hamsters. However, these correlations cannot be considered strong evidence for the hypothesis that reproductive status is directly determined by any single dimension of body size or composition. As we noted in our paper, the correlation between fatness and reproductive cyclicity is not always present, either in humans (*1*) or in rats (*2*).

More important, when tested directly, a critical fatness hypothesis is not supported. In Syrian hamsters, a particular body fat content is not necessary for the maintenance of estrous cycles as long as one or more metabolic fuels is supplied in the diet (*3, 4*). Conversely, a high body fat content is not sufficient for maintenance of estrous cycles when the availability of metabolic fuels is inhibited pharmacologically (*4*). The importance of the availability of metabolic fuels in the control of reproduction is supported by data from a wide phylogenetic range of species. In food-restricted, prepubertal male macaques, which normally have reduced circulating levels of luteinizing hormone (LH), LH levels increased after infusion with glucose and amino acids (*5*). The increase in LH was not correlated with body weight, weight gain, or age. In female rats in which puberty has been delayed by food restriction, LH pulsing characteristic of adults can be induced within 2 to 4 hours by allowing the animals to ingest a meal (*6*).

Thus, useful models relating nutrition and reproductive function must account for factors in addition to body weight and composition. A metabolic fuel hypothesis is consistent with the well-known correlation between fertility and body fat content, since adipose tissue is a storage depot for one of these fuels (fatty acids). There is no doubt that fatness and fertility are correlated. Nevertheless, it is conceivable that this correlation simply reflects the fact that both fuel storage in adipose tissues and reproduction require a supply of metabolic fuels over and above those necessary for maintenance of essential functions such as basal metabolism, thermoregulation, and locomotion.

With regard to Frisch's statement about whether it is appropriate to extrapolate conclusions in 85-gram hamsters to 57,000-gram humans, we hope that future research in this area will be guided by testable hypotheses based on strong inference rather than on purely correlational evidence, regardless of the body weight of the species studied.

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