NMR: A Critical Analysis

To the editor:

As an NMR spectroscopist, I would like to comment on the article "The Good, the Bad and the Indifferent" (*Bio/Technology* **11**: 36, January) by John Hodgson. The article contains numerous factual errors concerning NMR which I will point out. In fact, the title could apply to the subject matter or to the article itself!

1. NMR does not measure "vibrational energies in hydrogen atoms;" it detects nuclear transitions when a nucleus with a non-integral spin quantum number is placed in a magnetic field. *Other* nuclei besides protons are also detected. This is important, because we acquire the spectra of C-13 and N-15 to determine structures of large molecules. Isotopically labeled samples provide an increase in both the amount and the kind of structural data gathered. In addition to inter-proton distance measurement, torsion angles are also obtained from coupling constants.

2. Regions of protein mobility can be detected using measurements of C-13 and N-15 nuclei. The "spaghetti" effect may be due to very real mobility of the protein, and that mobility may have significance in how a given protein functions.

3. Angle nomenclature: Chi is the torsion around the C-alpha--C-beta bond, not the N--C-alpha bond.

4. The table comparing strengths and weaknesses of crystallography and NMR is misleading. For example, NMR structures obtained using isotopically C-13 and N-15 labeled proteins can have resolution very close to those obtained by crystallographic methods. NMR can obtain structure of proteins up to about 25 kD at present. Also, certain features of an active site structure can be obtained in great detail by NMR (Smith S.O., et al. *Science* **244**: 961). This is because the chemistry that occurs usually involves protons and protons are not detected by X-ray crystallographic methods, although they are seen with neutron diffraction.

5. Reference 5 was published in 1992, not 1991.

This article disappointed me because I was so impressed by the journal so much that only last week I ordered a personal subscription. Had I read this article first, I probably would not have placed that order. (By the way, how about a lower subscription rate for students and post-docs?)

Mr. Hodgson has a good point. Structural data should be critically analyzed, but then so should manuscripts! I personally would be happy to act as a reviewer.

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Erlich and the Magic Bullet

To the editor:

An issue of *Bio/Technology* that offers kudos to Paul Erlich twice (*Bio/Technology* **11**: 156, February) gives one pause to contemplate the sad fact that no one, hardly ever, strolls down memory lane to toss a wreath at von Pirquet and Schick. Who? Well, maybe it takes Paul Muni or Edward G. Robinson to immortalize a life's ouevre, but those of us who fancy historical immunology recall (sans movie-biog) the significance of the once near best-seller, *Das Serumkrankheit*, by von Pirquet and Schick (1905). Cast your mind back to the period where, despite the Erlich concept and the efforts of many to build the magic bullet, for many infectious diseases there were no successful therapeutic agents. (Not all that much has changed in treatment of non-bacterial pathogens in the last century.) The dramatic rescue of a child dying of diptheria toxin toxicity (although they didn't know about phage) or patients dying of pneumonia, depended on antisera. How many cinematic melodramas had happy endings only after the miraculous "serum" had been administered to the hero or heroine? Antisera were the only specific, targeted, and extremely helpful drugs in the physician's armamentarium. Generally, the magic bullets against diptheria toxin were produced by injecting horses with toxin and harvesting the serum to provide immediate passive immunization to patients in which the disease was diagnosed. However, von Pirquet's observations of the acute and serious illness (serum sickness) that followed the life-saving administration of diptheria antitoxin was a classic in the growing understanding of immunopathology. Von Piquet and Schick connected the disease to the time-frame in which the patient was developing antibodies to the horses antibodies against the toxin, now acting as antigen. The name given the disease has been modified, to give credit to the critter that produces the antibody/disease, i.e., HAMA (if von Pirquet had coined the term it would have been HAHA and who would have regarded him seriously?) These early studies also described the uses of minimal skin doses to determine individuals that had sensitivity to horse proteins and methods for desensitizing patients so that antitoxin could safely be given (in an era long before steroids) and where administration of horse serum intravenouly was the only life-saving measure. While our vocabulary increases in deluges, our conceptual advances come in trickles.

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