Editorial

The last year was a good one for *The Journal of General Physiology*. The number of submitted articles grew by 50%, and the median time from initial manuscript submission to publication was reduced to six months. Thanks to diligent efforts in the editorial office and at The Rockefeller University Press the number of manuscripts in review, under revision, or in press has been reduced to one half of the number received in a year. These accomplishments could not have been brought about without continued support from our referees, who still provide the constructively critical reviews that always have been a hallmark of *The Journal*, but now with a reduced turnaround time. We are most appreciative of their efforts, which are critical for the further evolution of *The Journal*.

As part of this evolution, abstracts of articles are available on The Rockefeller University Press World Wide Web site (http://www.rockefeller.edu/RUPress). The aim is to accelerate international distribution of the information in *The Journal*. Among the initiatives to be implemented in the coming year is an electronic version of *The Journal*: we will, for the time being, maintain the paper version of *The Journal*, but a WWW version will come online this year.

Readers of *The Journal* will have noted a broadening in the scope of the articles that we publish. In addition to articles in areas that have been the traditional mainstay of *The Journal*, we now publish articles dealing with problems that range from the strictly molecular to those of system physiology. This broadening in scope reflects the changes that are taking place in biological research, where the cloning and sequencing of an ever increasing number of proteins has set the stage for in-depth studies of function at all levels (from the molecular, to systems, to the whole body).

Systematic investigations of amino acid substitutions on protein function, and the use of amino acid replacement to probe accessibility, can now provide information about function and low-resolution structure. But a sine qua non for such studies is to have quantitative measures of protein function. These investigations therefore invariably become studies in molecular physiology. Mechanistic insights usually are obtained only when the results are interpreted using detailed model construction and analysis; we welcome such studies. Any such study, of course, is subject to the assumption that the amino acid replacements themselves do not significantly alter the protein dynamics. Unfortunately, given the myriad ways in which function can be altered, one sometimes wonders whether some of the more useful (although not normally publishable) findings may not be the identification of sequence positions that truly have no direct effect on function?

The advances in molecular biological methods also mean that one can begin to determine why, and how, a given protein is important for function at higher levels. Again, the implementation of such studies depends on having quantitative measures of complex functions. One could not, for example, understand how mutations in the α-subunit of the voltage-dependent sodium channel causes hyperkalemic periodic paralysis without a quantitative understanding of how the different voltage-dependent conductances in the muscle membrane interact to produce the propagated action potential. Nor would one understand why mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) are lethal without a clear understanding of the physiology of transepithelial fluid transport. Mechanistic insights into these and other complex problems often are achieved in the manner envisaged by Jacques Loeb and W.J.V. Osterhout when they founded *The Journal of General Physiology*, namely in studies at the interface between biology, chemistry, and physics.

Historically, mutations with clinical phenotypes have provided the material for numerous studies into both abnormal and normal biological function. Such genetic diseases have yielded important insights into the impact of the activities of specific molecules on the organisms as a whole. Nevertheless, these studies were "accidental" because they usually arose from spontaneous mutations rather than from a hypothesis-driven experimental design. The situation is changing rapidly, as transgenic and knockout animals allow

J. Gen. Physiol. © The Rockefeller University Press • 0022-1295/97/01/1/2 $2.00
Volume 109 January 1997 1–2

for hypothesis-driven studies of higher-order biological function. The interpretation of such studies depends upon the usual caveats — and the results may be unexpected, as when the mutation (or knockout) of an important protein leads to no apparent change in phenotype. Each new experimental model is a new organism, however, which may develop differently and have different adaptive characteristics than those of the wild-type parents. It therefore is imperative to undertake detailed investigations into how the genetic manipulation affects the function of the organism as a whole and, most importantly, of how the animal is able to adapt to experimental manipulations. By analogy with the lessons from cystic fibrosis and hyperkalemic periodic paralysis, fundamental insights are likely to depend upon quantitative studies of biological function. *The Journal of General Physiology* welcomes such studies that elucidate biological, chemical, or physical mechanisms of broad physiological significance.

Olaf Sparre Andersen
Editor
The Journal of General Physiology