On Not Being the Last to Give Up the Old or the First to Adopt the New

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As the Hypertension editorial office prepares to move to Jackson, Miss, those of us who have worked on the editorial staff can confidently say that we have learned a great deal from the experience. The opportunity to observe the scientific review process up close could not help but raise issues and questions for later consideration. One of the more interesting things about the past 8 years is the recognition that science has indeed progressed, that the field has been advanced in a meaningful way, and that Hypertension has played at least a small part in that progress by giving voice to the work of so many. Eight years ago, the biology of angiotensin type 1 and type 2 receptors was not well understood, the role of angiotensin-(1-7) was unclear, the benefits of ACE inhibitors in diabetes and vascular disease were unappreciated, and the utility of angiotensin receptor blockade was more a promise than a reality.1–4 Progress has been made in all these areas and many others. Medicine advances. The system does work.

On the other hand, one cannot help but wonder whether the system works optimally. The deliberate evaluation of new data, the careful honest skepticism that greets any new formulation of biology, and the continual demand for confirmatory data are all essential to orderly progress. This is particularly important in those areas of clinical research in which extremely stringent standards must be applied to results that could modify patient care. But could it be that in other areas the system sometimes is too slow to adopt the new, or that fashions are too hard to change? Perhaps I raise this question because of the extraordinarily high rejection rate that has been imposed on Hypertension of late and the realization that many important findings will be delayed in publication and then published only after another journal is found. Or perhaps it is the realization that given the explosive rate of advance that is likely to occur as the result of the continued application of modern biology to medicine, we are all going to have to learn to evaluate and, when appropriate, adopt the new in a much more rapid fashion than is now the case.

Let me present 2 case histories for consideration, not because they are particularly important but because I am familiar with them. The first of these is the concept of the tissue renin-angiotensin systems.5–7 First described by Boucher, Genest, Ganten, Hayduk and their colleagues, the idea that angiotensin could be formed in cardiovascular tissues was studied by many investigators.5 It aroused much controversy, especially regarding the possibility that in some cases, renin could be made in tissues. I can recall a particularly feisty exchange in the literature that Dr Victor Dzau and I engaged in to defend the existence of regulated angiotensin synthesis in tissues.6 But today, these systems are widely accepted. Few doubt that the regulated synthesis of angiotensin takes place in tissues, and there is even compelling evidence confirming the local synthesis of renin in specific circumstances in tissues, including cardiovascular tissue.8–12

The focus has now shifted to determining the precise role of these systems in health and disease and to identifying therapeutic strategies for the optimal use of ACE inhibitors and angiotensin receptor blockers. Progress has been made. But one wonders whether it could not have happened sooner. A second example is the idea that some peptide hormones (in particular, angiotensin) function in the intracellular space as well as at the external cell membrane. Unlike tissue angiotensin systems, this notion of intracellular angiotensin action is as yet unproven and unaccepted, although there is a growing body of data to support it. Indeed, there is a large body of evidence to support the idea that many peptide hormones and growth factors operate in an intracellular mode, a kind of hormone action that I have called intracrine.13 Whereas 20 years ago this idea was met with hostility, it is now simply greeted, in general, with quiet skepticism. This is progress, but given the data to support the idea, one wonders whether that progress could have come faster.

If these examples seem unconvincing, there are plenty of others that could be given from a variety of related disciplines. The idea that the bone marrow contains a population of more or less pluripotent stem cells was first proposed more than 20 years ago and was developed in carefully conducted studies. But only now is this idea accepted, developed, and applied.14,15 It was 30 years ago or so that a link between homocysteine and adult vascular disease was reported. Despite confirmatory studies over the years, only recently has this idea been accepted, developed, and applied.16 And the concept of inhibiting tumor angiogenesis had many ups and downs before arriving at its current position of quasi acceptability.17,18 Other examples could be given, but the point is clear. On the one hand, the present system works well and ensures (to the extent possible) that artifacts and frauds are not taken as science. On the other hand, it often does its work with a coarse brush. Can it be improved?

The heart and soul of today’s biomedical establishment is peer review. It is peer review that determines funding and determines publication. And funding and publication set the course of science. To the extent that the system is to be optimized, peer review must be optimized (the alternative of moving to a different kind of system is unappealing and possibly dangerous). This then raises the question of whether

(Hypertension. 2001;38:759-760.)
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759
and when peer review works less than optimally and of what factors lead to the acceptance or rejection of a grant, a paper, or an idea. This is itself a legitimate area for investigation. Because reviewers are human, there is, of course, the possibility that self-serving, excessively competitive, or even pecuniary thinking can enter into the process. Clearly, all reviewers on any panel must be on the lookout for this kind of behavior and suppress it when it is found. This is really a corollary to the now widespread realization that conflict of interest can raise its ugly head in clinical trials, in research lectures, in publications, and elsewhere. The press, government agencies such as the Food and Drug Administration, and others are keenly interested in problems of this sort. But with that said, it is unlikely that self-serving behavior is at the root of the phenomenon discussed here. There simply are too many people of integrity on study sections, review panels, and editorial boards for that to be the case. Rather, when it occurs, the phenomenon seems to be one of group-think, intellectual conformity, or wishing not to run counter to one or another authority or orthodoxy. It may be simply that it is easier to reject than accept, to say thumbs down rather than thumbs up. At its worst, it may be intellectual hubris.

But whatever it is, it is something that we must come to understand and be on the watch for. It is not that the world will end if we do not. It is that things will not work as well as they should and that progress will be delayed. And as modern biology provides increasingly novel results with increasing rapidity, it would not be good to accept that delay as simply business as usual.

Aside from findings that directly affect patient care, perhaps the real challenge that reviewers face is not rooting out the bad, which is generally straightforward and, in the worst case, happens spontaneously over time. Perhaps the real challenge is protecting the good.

In any event, that is how it looks to me as we in the editorial office try to avoid having to reject one more clearly meritorious paper. Let me close by saying that it has been a pleasure to have worked with so many creative and understanding investigators over the past 8 years. It has been an even greater pleasure to watch the editor of Hypertension, Dr Edward Frohlich, nurture and grow this fine publication to what it is today and to work with Dr Navar and our top-notch editorial staff.

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Hypertension. 2001;38:759-760
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/38/4/759

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